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(54) Title: COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: Provided herein are compounds and pharmaceutical compositions comprising said compounds that are useful for treating diseases. Specific diseases include those that are mediated by YAP/TAZ or those that are modulated by the interaction between YAP/TAZ and TEtOAcD.

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COMPOUNDS AND METHODS OF USE THEREOF

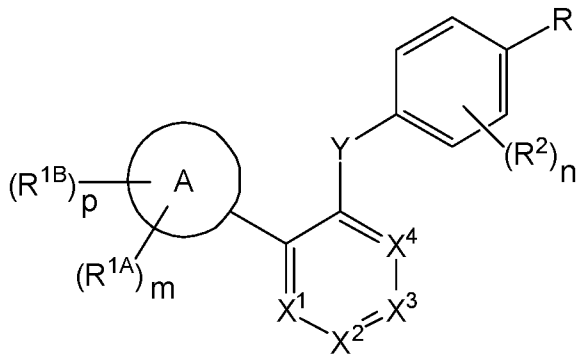
BACKGROUND OF THE DISCLOSURE

[0001] YAP and TAZ are transcriptional co-activators of the Hippo pathway network and regulate cell proliferation, migration, and apoptosis. Inhibition of the Hippo pathway promotes YAP/TAZ translocation to the nucleus, wherein YAP/TAZ interact with transcriptional enhancer associate domain (TEtOAcD) transcription factors and coactivate the expression of target genes and promote cell proliferation. Hyperactivation of YAP and TAZ and/or mutations in one or more members of the Hippo pathway network have been implicated in numerous cancers. Described herein are inhibitors associated with one or more members of the Hippo pathway network, such as inhibitors of YAP/TAZ or inhibitors that modulate the interaction between YAP/TAZ and TEtOAcD.

SUMMARY OF THE DISCLOSURE

[0002] Provided herein are compounds of Formula (I) and pharmaceutical compositions comprising said compounds. In some embodiments, the subject compounds are useful for the treatment of diseases or disorders. In some embodiments, the disease or disorder is cancer.

[0003] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl,

substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^4 and R^5 taken together with the atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

[0004] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0005] In another aspect, the present disclosure provides a compound described in Table 1, or a pharmaceutically acceptable salt or solvate thereof.

[0006] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable excipient.

[0007] In another aspect, the present disclosure provides a method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject in need thereof a a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[0008] In another aspect, the present disclosure provides a method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject has cancer, polycystic kidney disease, or liver fibrosis. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[0009] In another aspect, the present disclosure provides a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[0010] In another aspect, the present disclosure provides a method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

DETAILED DESCRIPTION OF THE DISCLOSURE

Certain Terminology

[0011] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.

[0012] As used herein, in some embodiments, ranges and amounts are expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 μL" means "about 5 μL" and also "5 μL." Generally, the term "about" includes an amount that is expected to be within experimental error.

[0013] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0014] As used herein, the terms "individual(s)", "subject(s)" and "patient(s)" mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g., constant or intermittent) of a health care worker (e.g., a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly, or a hospice worker).

[0015] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0016] "Amino" refers to the $-NH_2$ radical.

[0017] "Cyano" refers to the -CN radical.

[0018] "Nitro" refers to the $-NO_2$ radical.

[0019] "Oxa" refers to the -O- radical.

[0020] "Oxo" refers to the =O radical.

[0021] "Thioxo" refers to the =S radical.

[0022] "Imino" refers to the =N-H radical.

[0023] "Oximo" refers to the =N-OH radical.

[0024] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, OR^a, $-SR^a$, $OC(O)R^a$, $N(R^a)2$, $C(O)R^a$, $C(O)OR^a$, $C(O)N(R^a)_2$, $N(R^a)C(O)OR^f$, $OC(O)\ NR^aR^f$, $N(R^a)C(O)R^f$, $N(R^a)S(O)_tR^f$ (where t is 1 or 2), $S(O)tOR^a$ (where t is 1 or 2), $S(O)tR^f$ (where t is 1 or 2), and $S(O)tN(R^a)2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0025] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0026] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, OR^a, $-SR^a$,

OC(O) R^a, $N(R^a)2$, $C(O)R^a$, $C(O)OR^a$, $C(O)N(R^a)_2$, $N(R^a)C(O)OR^f$, OC(O) NR^aR^f, $N(R^a)C(O)R^f$, $N(R^a)S(O)_tR^f$ (where t is 1 or 2), $S(O)tOR^a$ (where t is 1 or 2), $S(O)tR^f$ (where t is 1 or 2), and $S(O)tN(R^a)2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0027] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl has two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, OR^a, $-SR^a$, OC(O) R^a, $N(R^a)2$, $C(O)R^a$, $C(O)OR^a$, $C(O)N(R^a)_2$, $N(R^a)C(O)OR^f$, OC(O) NR^aR^f, $N(R^a)C(O)R^f$, $N(R^a)S(O)_tR^f$ (where t is 1 or 2), $S(O)tOR^a$ (where t is 1 or 2), $S(O)tR^f$ (where t is 1 or 2), and $S(O)tN(R^a)2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0028] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In some embodiments, the points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In

other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, -OR^a, -SR^a, -$OC(O)$-R^a, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^f$, -$OC(O)$- NR^aR^f, -$N(R^a)C(O)R^f$, -$N(R^a)S(O)_tR^f$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tR^f$ (where t is 1 or 2), and -$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, and each R^f is independently alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl.

[0029] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin, and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -R^b-CN, -R^b-OR^a, -R^b-$OC(O)$-R^a, -R^b-$OC(O)$-OR^a, -R^b-$OC(O)$-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-$C(O)R^a$, -R^b-$C(O)OR^a$, -R^b-$C(O)N(R^a)_2$, -R^b-O-R^c-$C(O)N(R^a)_2$, -R^b-$N(R^a)C(O)OR^a$, -R^b-$N(R^a)C(O)R^a$, -R^b-$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2), and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl (optionally substituted with one or more halo groups), aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a

straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0030] "Aryloxy" refers to a radical bonded through an oxygen atom of the formula –O-aryl, where aryl is as defined above.

[0031] "Aralkyl" refers to a radical of the formula -R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0032] "Aralkenyl" refers to a radical of the formula –R^d-aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0033] "Aralkynyl" refers to a radical of the formula -R^e-aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0034] "Carbocyclyl" or "carbocycle" refers refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclyl from "heterocyclyl" rings or "heterocycles" in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, a carbocyclyl is a monocyclic carbocyclyl or a bicyclic carbocyclyl. In some embodiments, a carbocyclyl is a monocyclic carbocyclyl. Carbocyclyls are non-aromatic or aromatic. Non-aromatice carbocyclyls are saturated or partially unsaturated. In some embodiments, a carbocyclyl is a bicyclic carbocyclyl. In some embodiments, at least one of the two rings of a bicyclic carbocyclyl is aromatic. In some embodiments, both rings of a bicyclic carbocyclyl are aromatic. Carbocyclyl include aryls and cycloalkyls.

[0035] "Cycloalkyl" refers to a monocyclic or polycyclic aliphatic, fully saturated non-aromatic carbocyclyl, wherein each of the atoms forming the ring (i.e., skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups include groups having from 3 to 6 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C_3-C_6cycloalkyl.

Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. In certain embodiments, a cycloalkyl comprises three to eight carbon atoms (*e.g.*, C_3-C_8 cycloalkyl). In other embodiments, a cycloalkyl comprises three to seven carbon atoms (*e.g.*, C_3-C_7 cycloalkyl). In other embodiments, a cycloalkyl comprises three to six carbon atoms (*e.g.*, C_3-C_6 cycloalkyl). In other embodiments, a cycloalkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 cycloalkyl). In other embodiments, a cycloalkyl comprises three to four carbon atoms (*e.g.*, C_3-C_4 cycloalkyl). An unsaturated carbocyclyl is also referred to as "cycloalkenyl." Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term " cycloalkyl" is meant to include cycloalkyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, -CN, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0036] "Carbocycloalkylalkyl" refers to a radical of the formula $-R^c-$ cycloalkyl where R^c is an alkylene chain as defined above. The alkylene chain and the cycloalkyl radical are optionally substituted as defined above.

[0037] "Halo" or "halogen" refers to bromo, chloro, fluoro, or iodo substituents.

[0038] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

[0039] "Heterocyclyl" or "heterocycle" refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which include fused, spiro, or bridged ring systems in some embodiments. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. In some embodiments, the heterocyclyl is attached to the rest of the molecule through any atom of the ring(s).

[0040] "Heterocycloalkyl" refers to a cycloalkyl group in which one or more skeletal atoms of the cycloalkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. The term heterocycloalkyl also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C_2-C_{10}heterocycloalkyl. In another aspect, a heterocycloalkyl is a 5- to 10-membered C_4-C_9heterocycloalkyl. In another aspect, a heterocycloalkyl is a 4- to 7-membered C_3-C_6heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring. Unless stated otherwise specifically in the specification, the term "heterocycloalkyl" is meant to include heterocycloalkyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl,

optionally substituted heteroarylalkyl, -CN, -R^b-CN
, -R^b-OR^a, -R^b-OC(O)-R^a, -R^b-OC(O)-OR^a, -R^b-OC(O)-$N(R^a)_2$, -R^b-$N(R^a)_2$, -R^b-C(O)R^a, -R^b-C(O)O
R^a, -R^b-C(O)$N(R^a)_2$, -R^b-O-R^c-C(O)$N(R^a)_2$, -R^b-$N(R^a)$C(O)OR^a, -R^b-$N(R^a)$C(O)R^a, -R^b-$N(R^a)S(O)_t$
R^a (where t is 1 or 2), -R^b-$S(O)_tOR^a$ (where t is 1 or 2), -R^b-$S(O)_tR^a$ (where t is 1 or 2),
and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0041] "Heteroalkyl" refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (e.g. –NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C_1-C_6heteroalkyl. In some embodiments, the alkyl part of the heteroalkyl radical is optionally substituted as defined for an alkyl group.

[0042] "Heterocycloalkylalkyl" refers to a radical of the formula –R^c-heterocycloalkyl where R^c is an alkylene chain as defined above. If the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, the heterocycloalkyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocycloalkylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocycloalkyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocycloalkyl group.

[0043] "Heterocycloalkylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c- heterocycloalkyl where R^c is an alkylene chain as defined above. If the heterocycloalkyl is a nitrogen-containing heterocycloalkyl, the heterocycloalkyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocycloalkylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocycloalkyl part of the heterocycloalkylalkoxy radical is optionally substituted as defined above for a heterocycloalkyl group.

[0044] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen, and sulfur. As used herein, in some embodiments, the heteroaryl radical is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally

quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pyridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or

2), and -R^b-$S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl, fluoroalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, or heteroarylalkyl, each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0045] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0046] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0047] "Heteroaryloxy" refers to radical bonded through an oxygen atom of the formula –O-heteroaryl, where heteroaryl is as defined above.

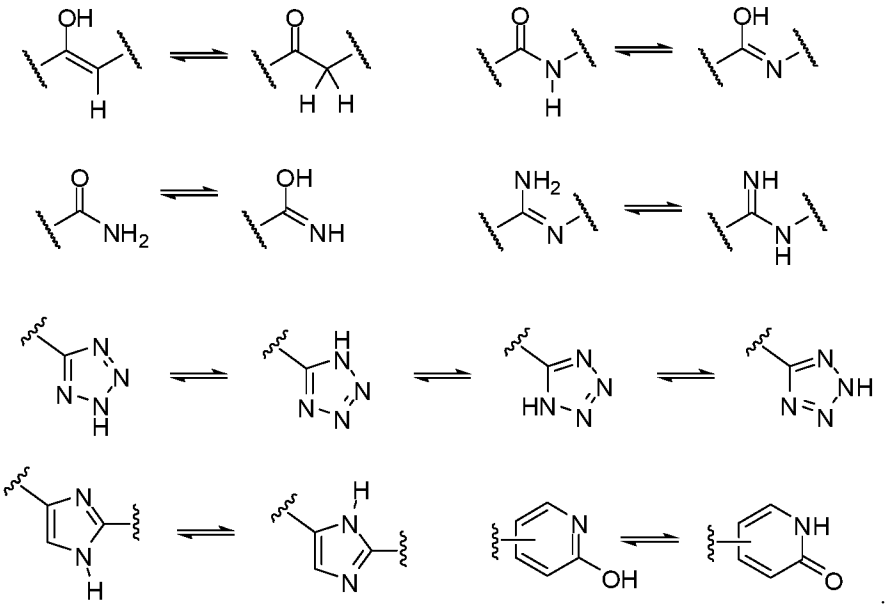
[0048] "Heteroarylalkyl" refers to a radical of the formula –R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0049] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0050] In some embodiments, the compounds disclosed herein contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and Z geometric isomers (*e.g., cis* or *trans*). Likewise, all possible isomers, as well as their racemic and optically pure forms,

and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or Z geometric isomers (*e.g., cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho-*, *meta-*, and *para-* isomers around a benzene ring.

[0051] A "tautomer" refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0052] "Optional" or "optionally" means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0053] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s). In some other embodiments, optional substituents are individually and independently selected from D, halogen, -CN, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -OH, =O, -CO_2H, -CO_2alkyl, -$C(=O)NH_2$, -C(=O)NH(alkyl), -$C(=O)N(alkyl)_2$, -$S(=O)_2NH_2$, -$S(=O)_2$NH(alkyl), -$S(=O)_2N(alkyl)_2$, -CH_2CO_2H, -CH_2CO_2alkyl, -$CH_2C(=O)NH_2$, -$CH_2C(=O)$NH(alkyl), -$CH_2C(=O)N(alkyl)_2$, -$CH_2S(=O)_2NH_2$, -$CH_2S(=O)_2$NH(alkyl), -$CH_2S(=O)_2N(alkyl)_2$, alkyl, alkenyl, alkynyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide,

arylsulfoxide, alkylsulfone, and arylsulfone. In some embodiments, optional substituents are individually and independently selected from D, halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, =O, $-CO_2H$, $-CO_2(C_1$-C_4alkyl), $-C(=O)NH_2$, $-C(=O)NH(C_1$-C_4alkyl), $-C(=O)N(C_1$-C_4alkyl$)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(C_1$-C_4alkyl), $-S(=O)_2N(C_1$-C_4alkyl$)_2$, C_1-C_4alkyl, C_3-C_6cycloalkyl, C_1-C_4fluoroalkyl, C_1-C_4heteroalkyl, C_1-C_4alkoxy, C_1-C_4fluoroalkoxy, $-SC_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, and $-S(=O)_2C_1$-C_4alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, -OH, =O, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, optional substituents are independently selected from D, halogen, -CN, $-NH_2$, -OH, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, optional substituents are independently selected from D, F, Cl, -CN, $-NH_2$, -OH, =O, $-NH(CH_3)$, $-N(CH_3)_2$, $-CH_3$, $-CH_2CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$. In some embodiments, substituted groups are substituted with one to six of the preceding groups. In some embodiments, substituted groups are substituted with one to four of the preceding groups.In some embodiments, substituted groups are substituted with one to three of the preceding groups. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, substituted groups are substituted with one of the preceding groups.

[0054] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Pharmaceutically acceptable salts of the compounds described herein are optionally pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0055] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic

acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997), which is hereby incorporated by reference in its entirety). In some embodiments, acid addition salts of basic compounds are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0056] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. In some embodiments, pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts, and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins, and the like. See Berge et al., *supra*.

[0057] As used herein, "treatment" or "treating " or "palliating" or "ameliorating" are used interchangeably herein. These terms refer to an approach for obtaining beneficial or desired results including, but not limited to, therapeutic benefit and/or a prophylactic benefit. By "therapeutic benefit" is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is

observed in the patient, notwithstanding that the patient is afflicted with the underlying disorder in some embodiments. For prophylactic benefit, in some embodiments, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

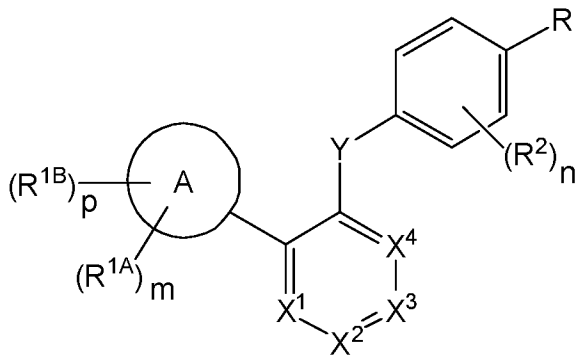
[0058] "Prodrug" is meant to indicate a compound that is converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. In some embodiments, a prodrug is inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

[0059] A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

[0060] The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. In some embodiments, prodrugs of an active compound, as described herein, are prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino, or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino, or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate, and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

Compounds

[0061] In one aspect, the present disclosure provides a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^2 is independently halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or

unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^4 and R^5 taken together with the atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

[0062] In some embodiments, ring A is 8- to 12- membered fused bicyclic heteroaryl.

[0063] In some embodiments, ring A is 9- to 11- membered fused bicyclic heteroaryl.

[0064] In some embodiments, ring A is 6/5-fused, 6/6-fused, or 6/7-fused bicyclic heteroaryl. In some embodiments, ring A is 6/5-fused or 6/6-fused bicyclic heteroaryl. In some embodiments, ring A is 6/5-fused or 6/7-fused bicyclic heteroaryl. In some embodiments, ring A is 6/6-fused or 6/7-fused bicyclic heteroaryl. In some embodiments, ring A is 6/5-fused bicyclic heteroaryl. In some embodiments, ring A is 6/6-fused bicyclic heteroaryl. In some embodiments, ring A 6/7-fused bicyclic heteroaryl.

[0065] In some embodiments, ring A is fused bicyclic heteroaryl having 1-6 heteroatoms, each independently selected from N, O, and S.

[0066] In some embodiments, ring A is fused bicyclic heteroaryl having 0-5 N atoms, 0-2 O atoms, and 0-2 S atoms. The compound of any one of claims 1-8, wherein ring A is fused bicyclic heteroaryl having 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 0-3 N atoms and 0-1 O atom. In some embodiments, ring A is fused bicyclic heteroaryl having 2 N atoms and 1 S atom. In some embodiments, ring A is fused bicyclic heteroaryl having 1 N atom and 1 O atom. In some embodiments, ring A is fused bicyclic heteroaryl having 1 N atom, 1 S atom, and 1 O atom.

[0067] In some embodiments, ring A is fused bicyclic heteroaryl having 1-5 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 1-4 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 1-3 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 1-2 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 2-

5 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 2-4 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 2-3 N atoms.

[0068] In some embodiments, ring A is fused bicyclic heteroaryl having 1 N atom. In some embodiments, ring A is fused bicyclic heteroaryl having 2 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 3 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 4 N atoms. In some embodiments, ring A is fused bicyclic heteroaryl having 5 N atoms.

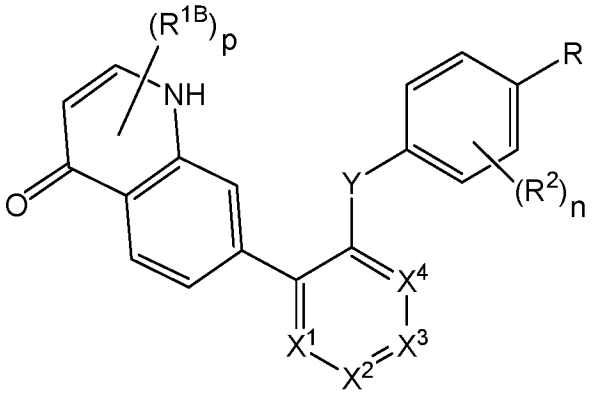
[0069] In some embodiments, ring A is 6/5-fused bicyclic heteroaryl selected from [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-6-yl, [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-7-yl, benzo[d]isoxazol-3(2H)-one-5-yl, benzo[d]isoxazol-3(2H)-one-6-yl, 3H-[1,2,3]triazolo[4,5-b]pyridine-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridine-6-yl, 1H-benzo[d][1,2,3]triazol-5-yl, 1H-benzo[d][1,2,3]triazol-6-yl, 1H-benzo[d]imidazol-5-yl, 1H-benzo[d]imidazol-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, 1H-imidazo[4,5-b]pyridin-5-yl, or 1H-imidazo[4,5-b]pyridin-6-yl.

[0070] In some embodiments, ring A is 6/5-fused bicyclic heteroaryl selected from [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-6-yl, [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-7-yl, 3H-[1,2,3]triazolo[4,5-b]pyridine-5-yl, 3H-[1,2,3]triazolo[4,5-b]pyridine-6-yl, [1,2,4]triazolo[4,3-a]pyridin-6-yl, [1,2,4]triazolo[4,3-a]pyridin-7-yl, 1H-imidazo[4,5-b]pyridin-5-yl, or 1H-imidazo[4,5-b]pyridin-6-yl.

[0071] In some embodiments, ring A is 6/6-fused bicyclic heteroaryl selected from quinolin-4(1H)-one-6-yl, quinolin-4(1H)-one-7-yl, isoquinolin-6-yl, isoquinolin-7-yl, cinnoline-6-yl, cinnoline-7-yl, quinazoline-6-yl, quinazoline-7-yl, quinazolin-4(1H)-one-6-yl, quinazolin-4(1H)-one-7-yl, 1,6-naphthyridin-4(1H)-one-7-yl, 1,8-naphthyridin-4(1H)-one-6-yl, 1,8-naphthyridin-4(1H)-one-7-yl, and 1,8-naphthyridin-4(1H)-one-6-yl.

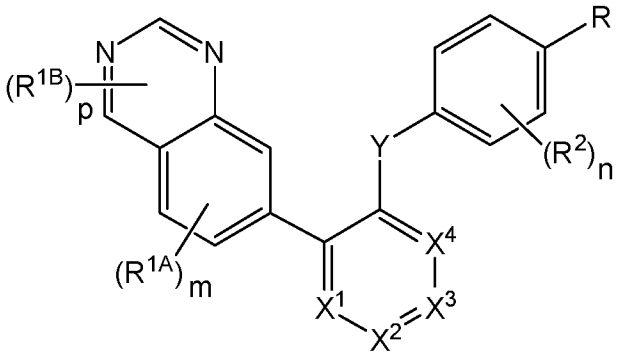
[0072] In some embodiments, ring A is 6/6-fused bicyclic heteroaryl selected from cinnoline-6-yl, cinnoline-7-yl, quinazoline-6-yl, quinazoline-7-yl, quinazolin-4(1H)-one-6-yl, quinazolin-4(1H)-one-7-yl, 1,6-naphthyridin-4(1H)-one-7-yl, 1,8-naphthyridin-4(1H)-one-6-yl, 1,8-naphthyridin-4(1H)-one-7-yl, and 1,8-naphthyridin-4(1H)-one-6-yl.

[0073] In some embodiments, the compound has a structure of Formula (II-a), or a pharmaceutically acceptable salt or solvate thereof:



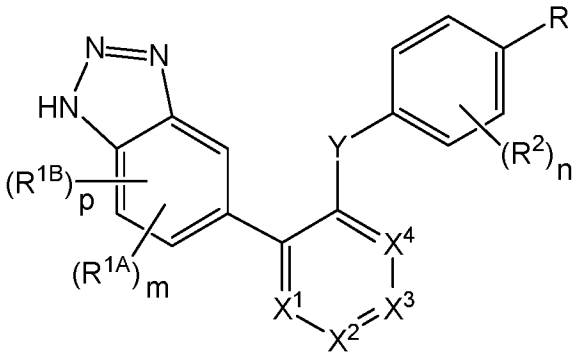
Formula (II-a).

[0074] In some embodiments, the compound has a structure of Formula (II-b), or a pharmaceutically acceptable salt or solvate thereof:



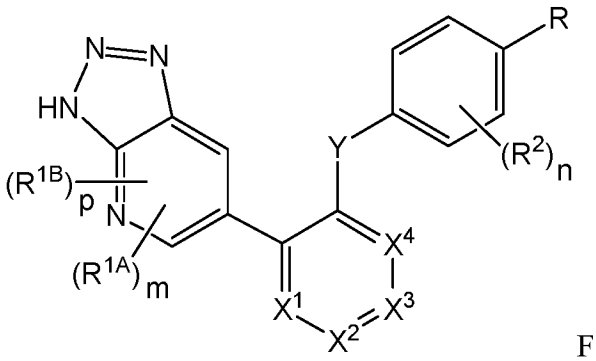
Formula (II-b).

[0075] In some embodiments, the compound has a structure of Formula (II-c), or a pharmaceutically acceptable salt or solvate thereof:



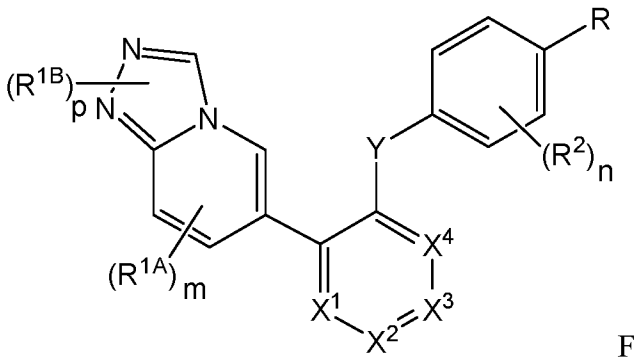
Formula (II-c).

[0076] In some embodiments, the compound has a structure of Formula (II-d), or a pharmaceutically acceptable salt or solvate thereof:



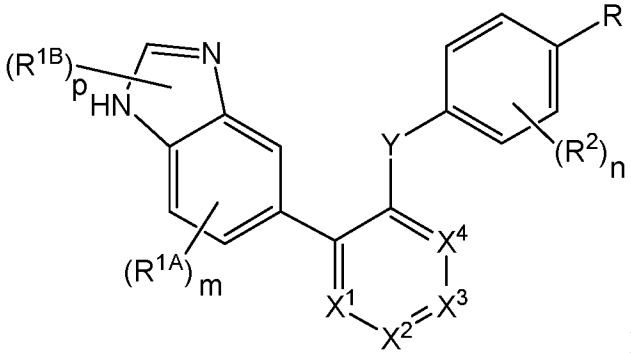
Formula (II-d).

[0077] In some embodiments, the compound has a structure of Formula (II-e), or a pharmaceutically acceptable salt or solvate thereof:



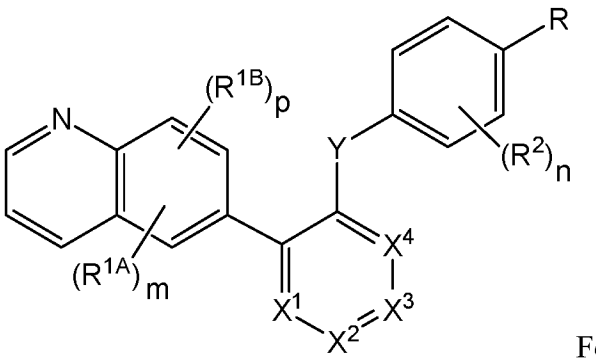
Formula (II-e).

[0078] In some embodiments, the compound has a structure of Formula (II-f), or a pharmaceutically acceptable salt or solvate thereof:



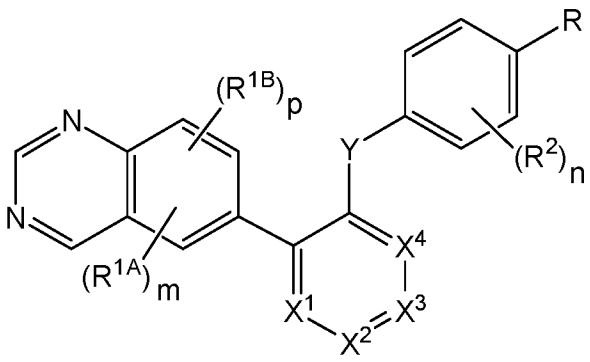
Formula (II-f).

[0079] In some embodiments, the compound has a structure of Formula (II-g), or a pharmaceutically acceptable salt or solvate thereof:



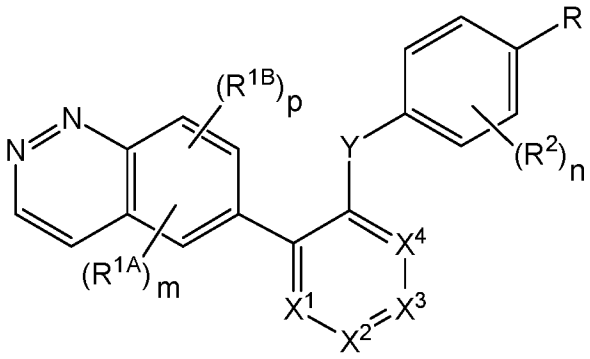
Formula (II-g).

[0080] In some embodiments, the compound has a structure of Formula (II-h), or a pharmaceutically acceptable salt or solvate thereof:



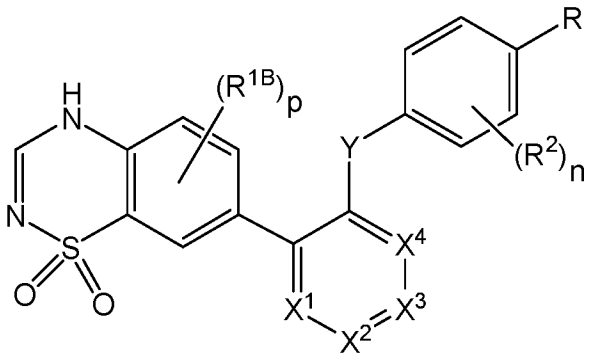
Formula (II-h).

[0081] In some embodiments, the compound has a structure of Formula (II-i), or a pharmaceutically acceptable salt or solvate thereof:



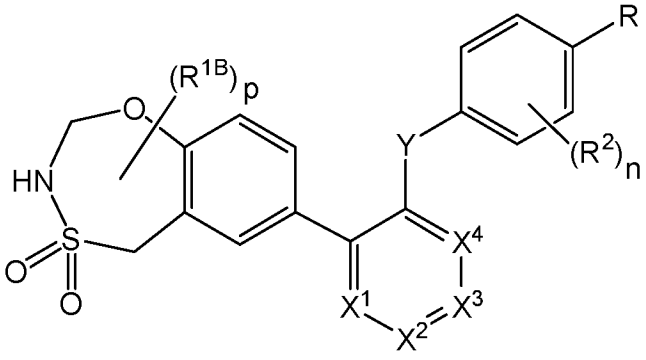
Formula (II-i).

[0082] In some embodiments, the compound has a structure of Formula (II-j), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-j).

[0083] In some embodiments, the compound has a structure of Formula (II-k), or a pharmaceutically acceptable salt or solvate thereof:

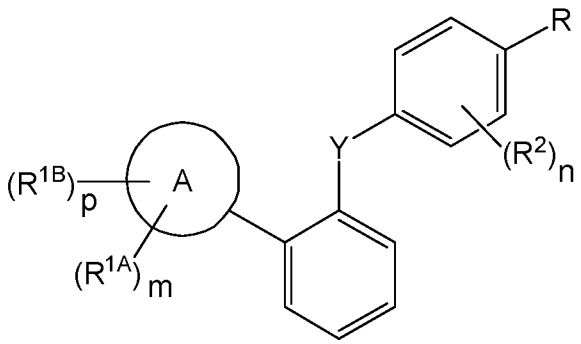


Formula (II-k).

[0084] In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is N; and X^4 is CR^{X4}. In some embodiments, X^1 is CR^{X1}; X^2 is N; X^3 is X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is N. In some embodiments, X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is N.

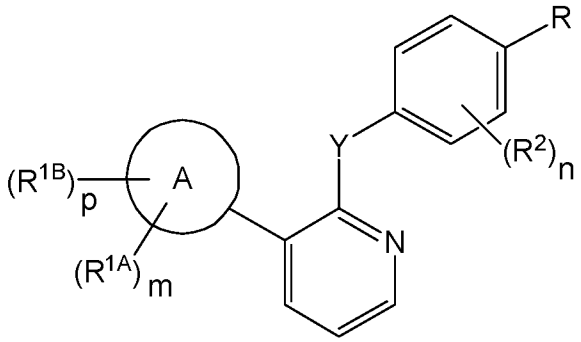
[0085] In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(OH)CH_3$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-C\equiv CH$, $-OCH_3$, $-NH_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-S(=O)CH_3$, or $-S(=O)_2CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-OCH_3$, or $-OCF_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, or $-CH_3$. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen or F. In some embodiments, each of R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is hydrogen.

[0086] In some embodiments, the compound has a structure of Formula (III-a), or a pharmaceutically acceptable salt or solvate thereof:



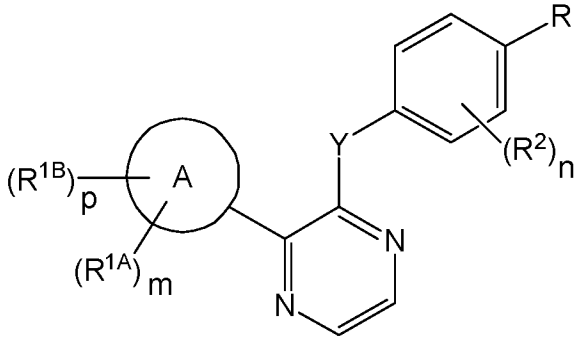
Formula (III-a).

[0087] In some embodiments, the compound has a structure of Formula (III-b), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-b).

[0088] In some embodiments, the compound has a structure of Formula (III-c), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-c).

[0089] In some embodiments, each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl.

[0090] In some embodiments, each R^{1A} and R^{1B} is independently halogen, oxo, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl.

[0091] In some embodiments, each R^{1A} and R^{1B} is independently F, Cl, Br, I, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CHFCH_3$, $-CF_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, or oxetan-3-yl.

[0092] In some embodiments, each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2CH_2NH_2$, $-CH_2CH_2CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CHFCH_3$, $-CF_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, or oxetan-3-yl.

[0093] In some embodiments, F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CHFCH_3$, $-CF_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, or oxetan-3-yl.

[0094] In some embodiments, F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, or oxetan-3-yl.

[0095] In some embodiments, each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

[0096] In some embodiments, each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, or $-OCH_3$.

[0097] In some embodiments, each R^{1A} and R^{1B} is independently -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, or $-CH_2CH(OH)CH_2OH$.

[0098] In some embodiments, each R^{1A} and R^{1B} is independently $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, or $-CH_2C(=O)N(CH_3)_2$.

[0099] In some embodiments, each R^{1A} and R^{1B} is independently $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, or oxetan-3-yl.

[00100] In some embodiments, R^{1A} is oxo. In some embodiments, R^{1A} is oxo and m is 1 or 2.

[00101] In some embodiments, R^{1B} is oxo. In some embodiments, R^{1B} is oxo and p is 1 or 2.

[00102] In some embodiments, m is 0, 1, 2, 3, or 4. In some embodiments, m is 0, 1, 2, or 3. In some embodiments, m is 0, 1, or 2. In some embodiments, m is 1 or 2. In some embodiments, m is 0 or 1. In some embodiments, m is 0. In some embodiments, m is 1. In some embodiments, m is 2.

[00103] In some embodiments, p is 0, 1, 2, 3, or 4. In some embodiments, p is 0, 1, 2, or 3. In some embodiments, p is 0, 1, or 2. In some embodiments, p is 1 or 2. In some embodiments, p is 0 or 1. In some embodiments, p is 0. In some embodiments, p is 1. In some embodiments, p is 2.

[00104] In some embodiments, each of m and p is independently is 0, 1, or 2.

[00105] In some embodiments, each of m and p is 1. In some embodiments, m is 2 and p is 0, 1 or 2. In some embodiments, m is 2 and p is 0 or 1. In some embodiments, m is 0 and p is 1. In some embodiments, each of m and p is 0.

[00106] In some embodiments, R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7S(=O)_2R^7$, $-NR^7C(=O)R^7$, $-NR^7C(=O)OR^7$, or substituted or unsubstituted C_1-C_6fluoroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, R is F, Cl, Br, I, nitro, -CN, $-SF_5$, $-SCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-C(=O)CH_3$, $-C(=O)OCH_3$ $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, R is F, Cl, -CN, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-OCF_3$, $-CHF_2$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-SF_5$, $-SCF_3$, or $-CF_3$. In some embodiments, R is F, Cl, $-SF_5$, $-OCF_3$, $-SCF_3$, or $-CF_3$. In some embodiments, R is $-SF_5$, $-SCF_3$, or $-OCF_3$. In some embodiments, R is $-SF_5$, $-SCF_3$, or $-CF_3$. I n some embodiments, R is $-CF_3$, $-SCF_3$, or $-OCF_3$. In

some embodiments, R is -OCF_3. In some embodiments, R is -CF_3. In some embodiments, R is -SF_5. In some embodiments, R is -SCF_3.

[00107] In some embodiments, each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)_2R^7$, -NR^7R^8, -$C(=O)OR^7$, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; and each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S. In some embodiments, each R^2 is independently F, Cl, Br, -CN, -OH, -OCH_3, -OCH_2CH_3, -OCH_2CH_2OH, -OCH_2CN, -OCF_3, -$S(=O)_2CH_3$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)OCH_3$, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, or -CF_3. In some embodiments, each R^2 is independently F, Cl, -CN, -OCH_3, -OCF_3, -$C(=O)OCH_3$, -CH_3, or -CF_3. In some embodiments, each R^2 is independently F, Cl, -OCF_3, or -CF_3. In some embodiments, each R^2 is independently F or Cl.

[00108] In some embodiments, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 1 or 2. In some embodiments, n is 0 or 1. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2.

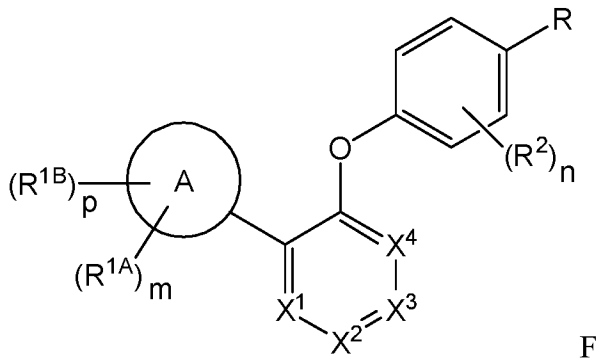
[00109] In some embodiments, Y is CR^4R^5, O, S, or NR^6. In some embodiments, Y is O, S, or NR^6. In some embodiments, Y is CR^4R^5, S, or NR^6. In some embodiments, Y is CR^4R^5, O, or NR^6. In some embodiments, Y is CR^4R^5, O, or S. In some embodiments, Y is CR^4R^5 or O. In some embodiments, Y is CR^4R^5 or S. In some embodiments, Y is CR^4R^5 or NR^6. In some embodiments, Y is O or S. In some embodiments, Y is O or NR^6. In some embodiments, Y is S or NR^6.

[00110] In some embodiments, Y is CR^4R^5. In some embodiments, each R^4 and R^5 is independently hydrogen or C_1-C_4 alkyl. In some embodiments, each R^4 and R^5 is hydrogen. In some embodiments, each R^4 is hydrogen and R^5 is -CH_3. In some embodiments, each R^4 and R^5 is -CH_3.

[00111] In some embodiments, Y is O or S. In some embodiments, Y is O. In some embodiments, Y is S.

[00112] In some embodiments, Y is NR^6. In some embodiments, R^6 is hydrogen or C_1-C_4 alkyl. In some embodiments, R^6 is hydrogen or $-CH_3$. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is $-CH_3$. In some embodiments, R^6 is $-OCH_3$. In some embodiments, R^6 is $-OCH_2CH_3$.

[00113] In another aspect, provided herein are compounds having a structure of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV).

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^2 is independently halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted

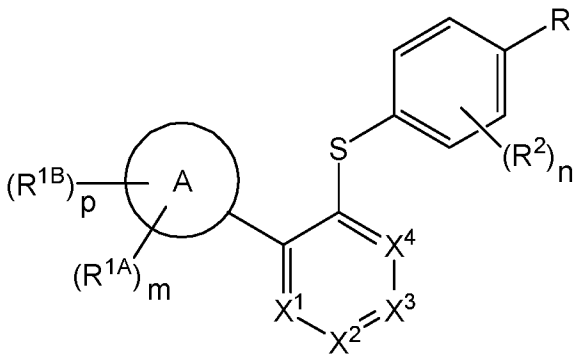
or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

[00114] In another aspect, the present disclosure provides a compound of Formula (V), or a pharmaceutically acceptable salt or solvate thereof:



Formula (V)

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -C(=O)R^7, -C(=O)NR^7R^8, -C(=O)OR^7, -S(=O)R^7, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -C(=O)R^7, -C(=O)NR^7R^8, -C(=O)OR^7, -S(=O)R^7, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, -OR^7, -SR^7, -S(=O)R^7, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -C(=O)R^7, -C(=O)OR^7, -C(=O)NR^7R^8, substituted or

unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

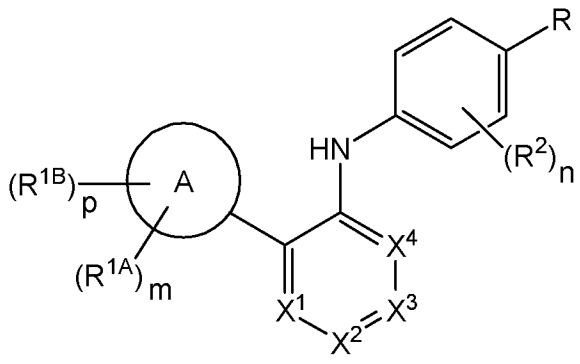
each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

[00115] In another aspect, the present disclosure provides a compound of Formula (VI), or a pharmaceutically acceptable salt or solvate thereof:



Formula (VI)

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, -OR^7, -SR^7, -CN, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl,

substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -NR^7R^8, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

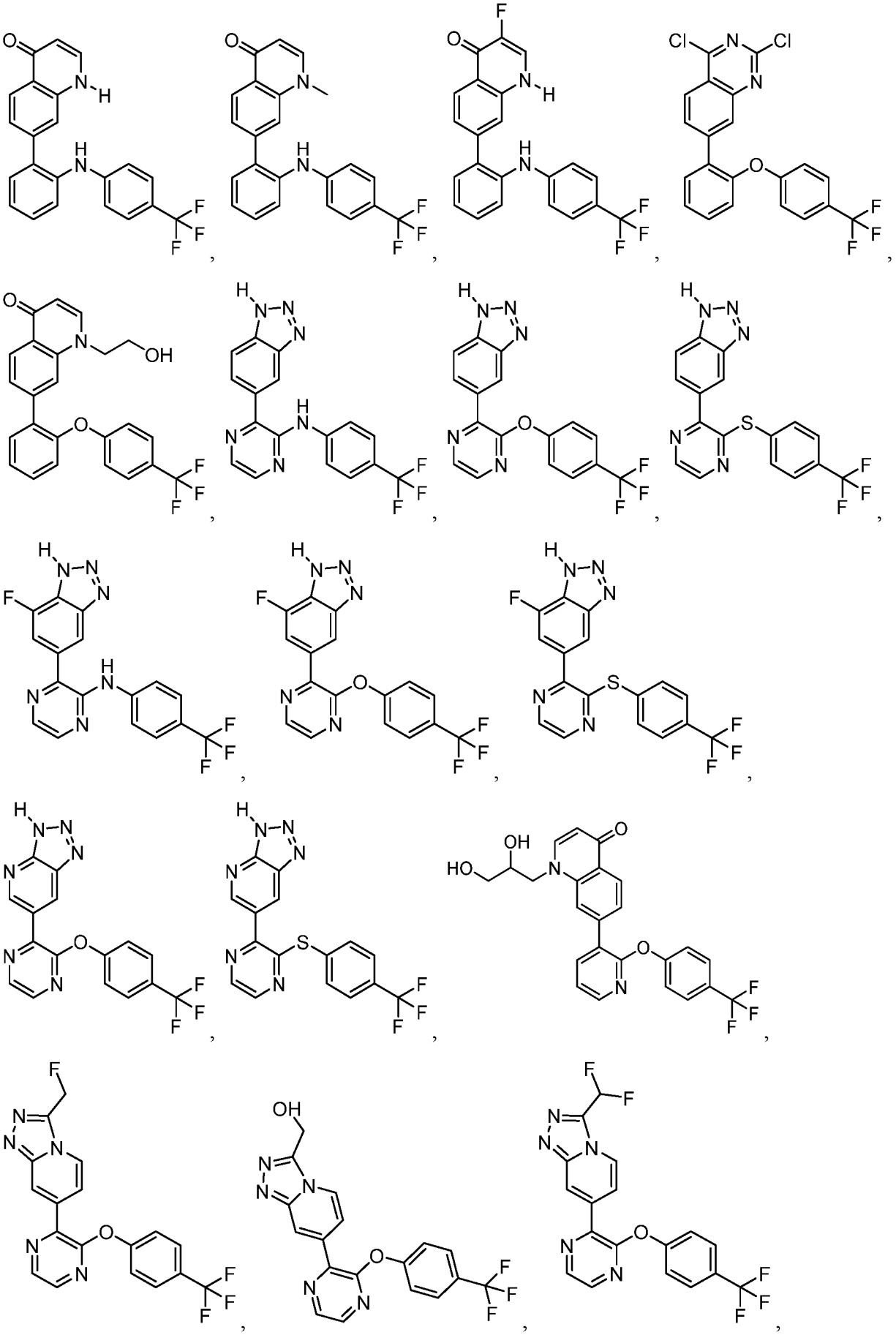
each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)R^7$, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -$C(=O)R^7$, -$C(=O)OR^7$, -$C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

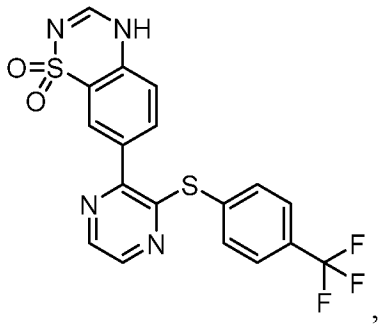
each R^7 and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

[00116] In certain embodiments, the compound of Formula (I) is selected from the group consisting of:

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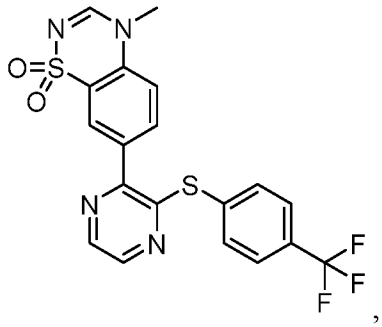
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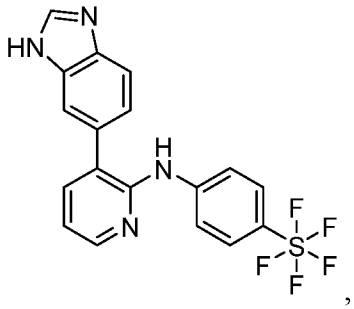
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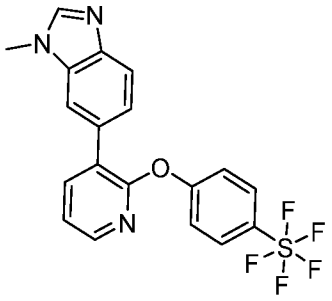
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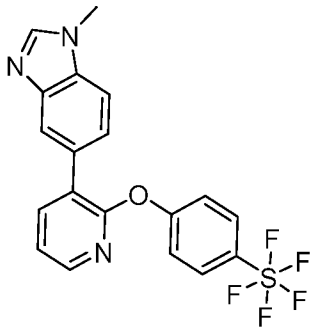
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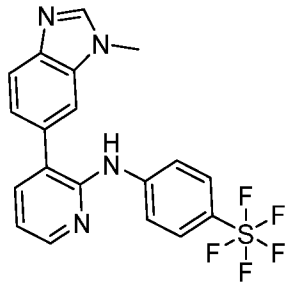
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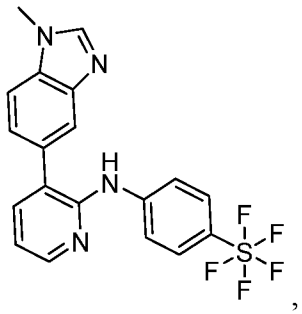
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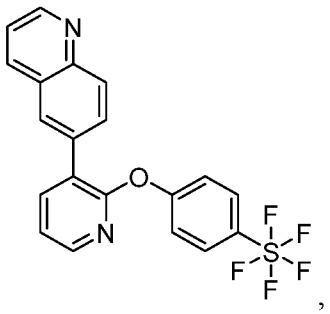
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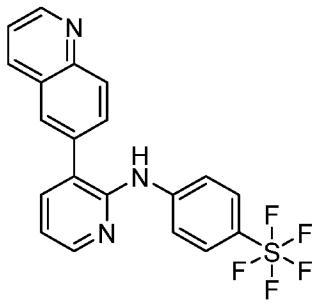
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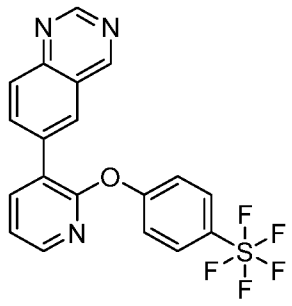
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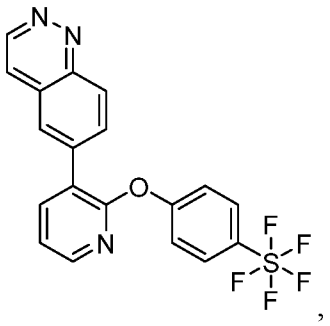
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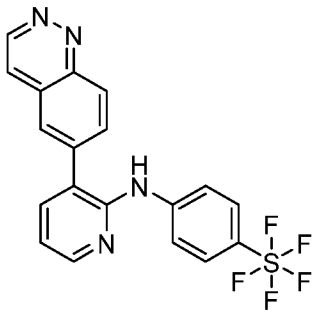
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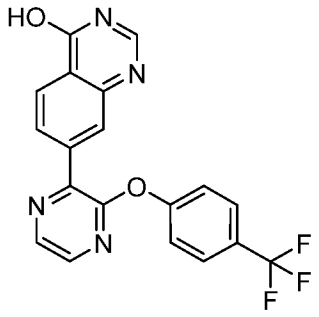
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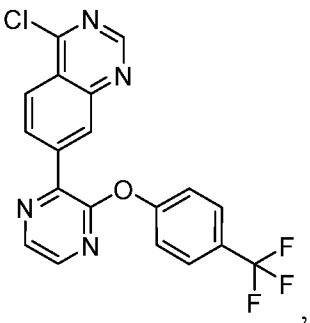
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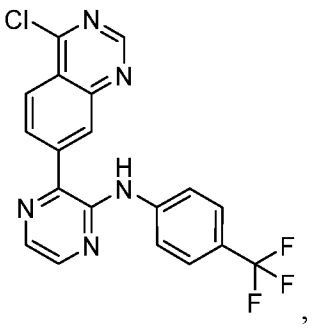
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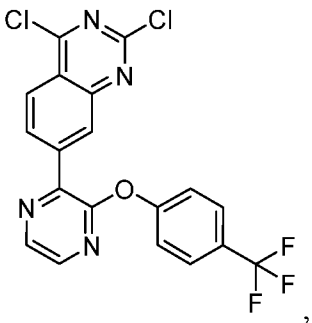
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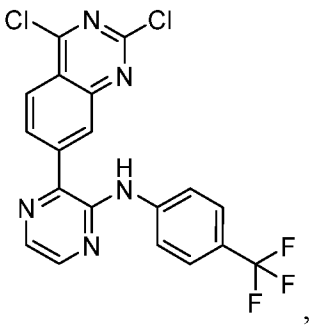
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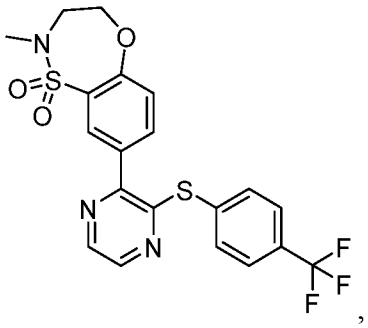
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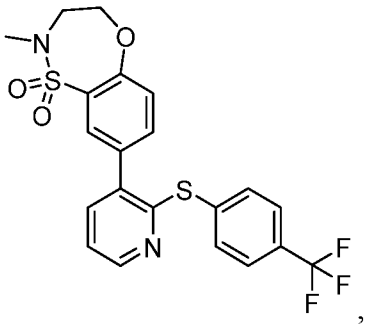
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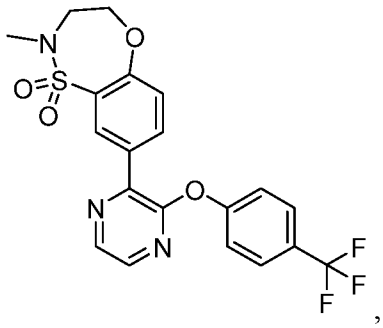
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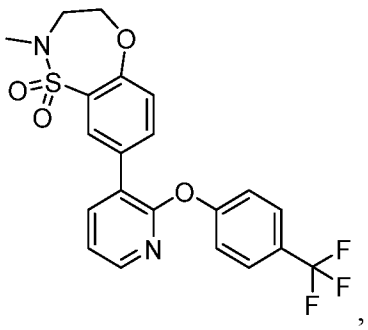
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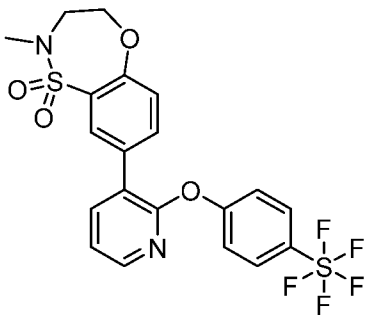
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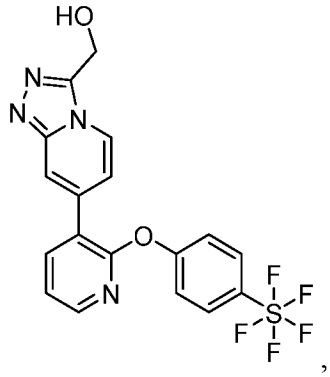
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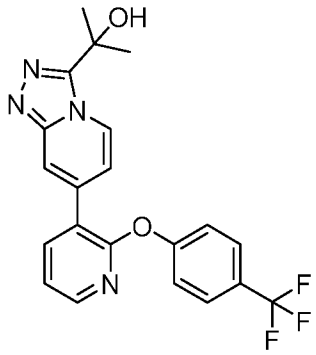
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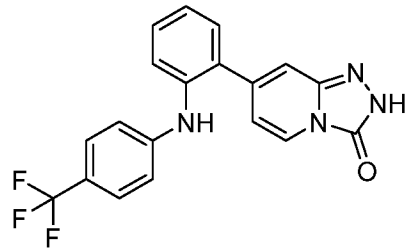
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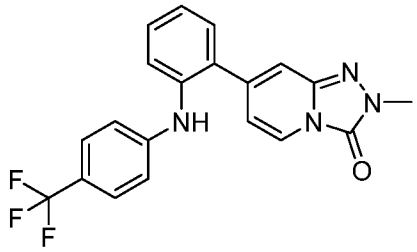
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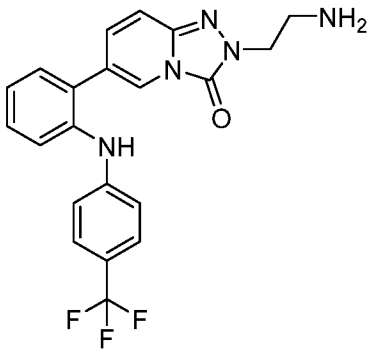
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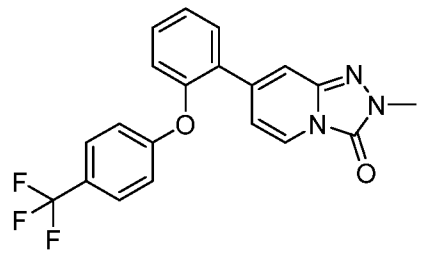
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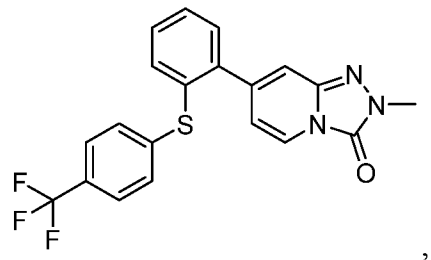
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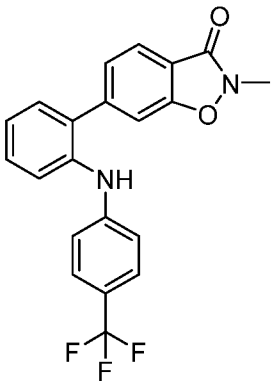
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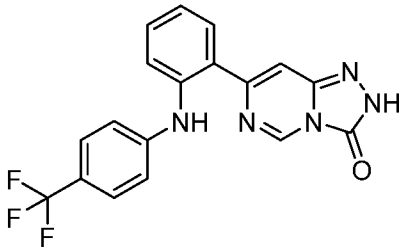
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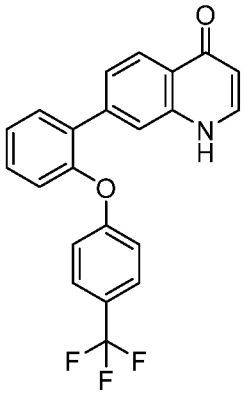
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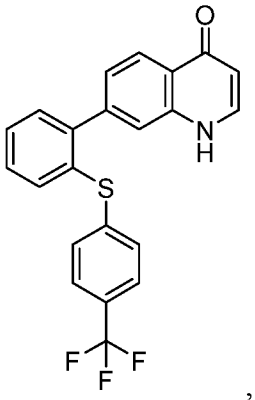
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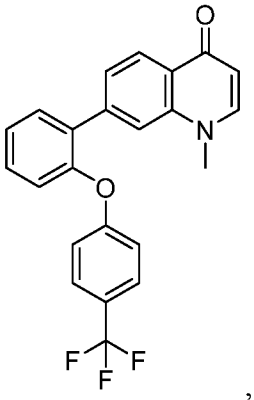
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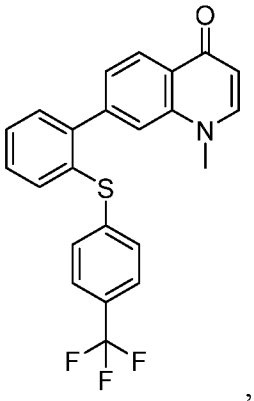
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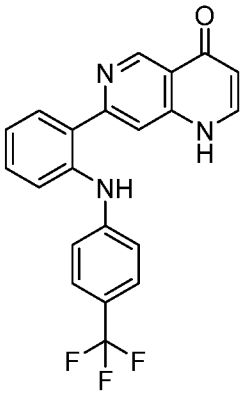
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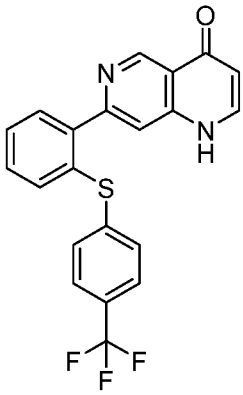
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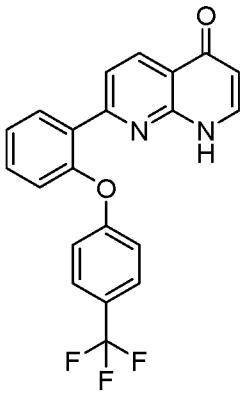
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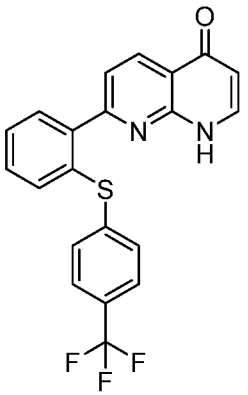
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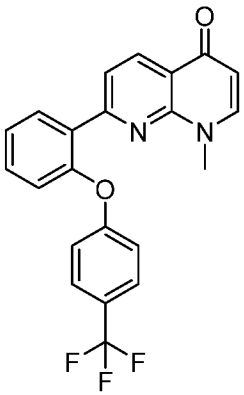
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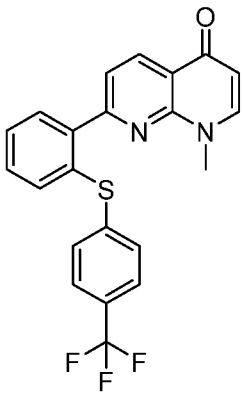
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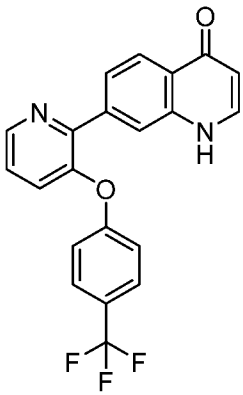
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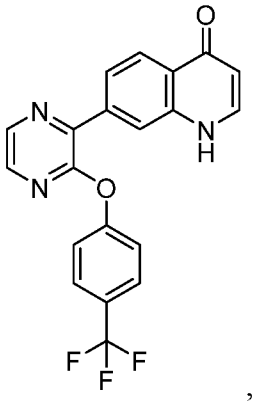
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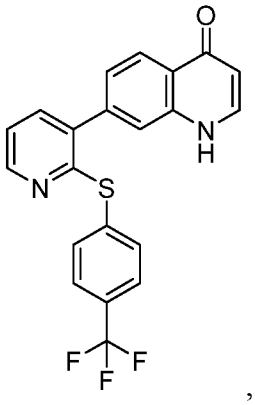
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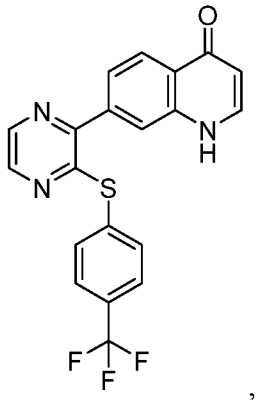
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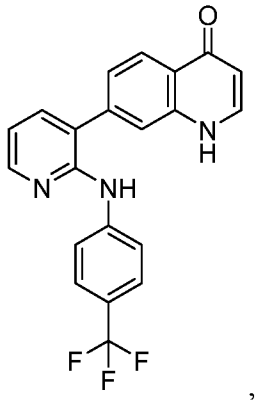
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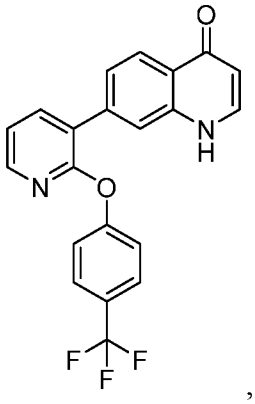
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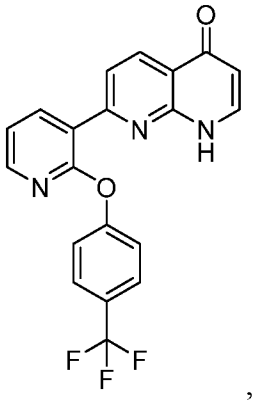
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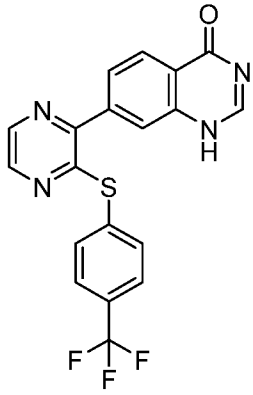
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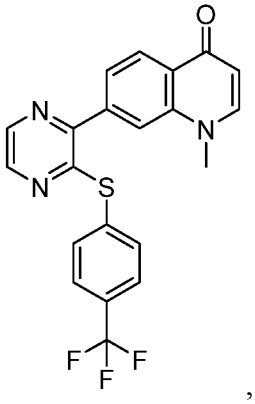
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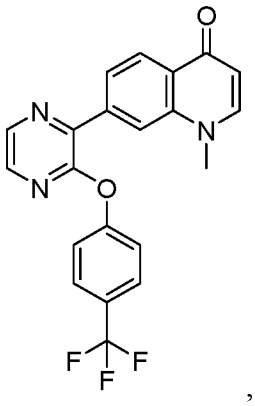
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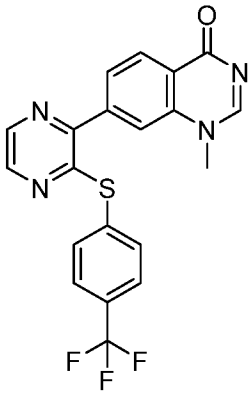
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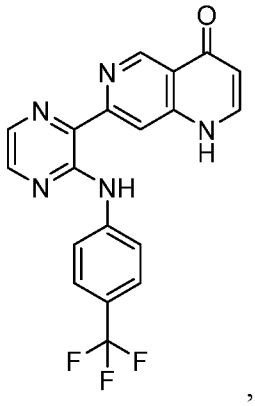
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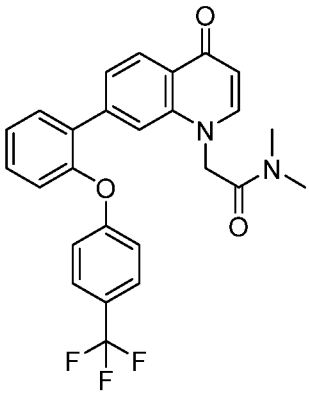
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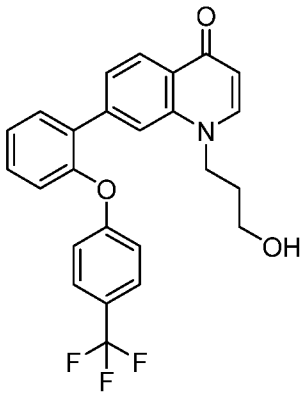
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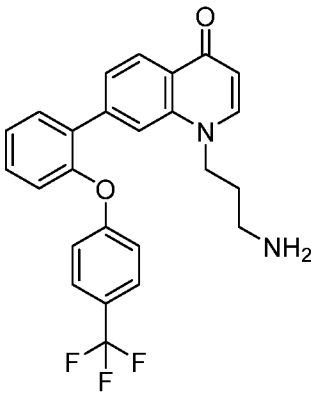
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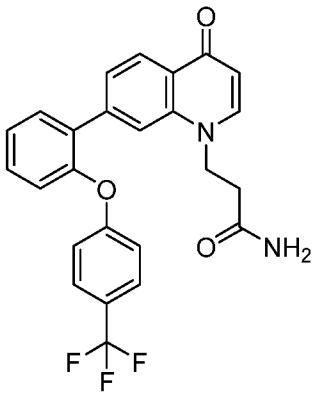
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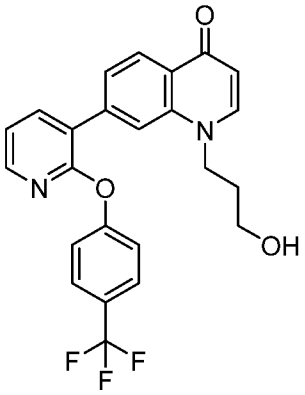
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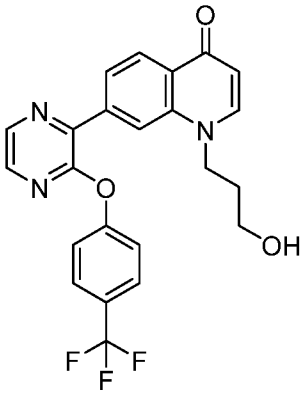
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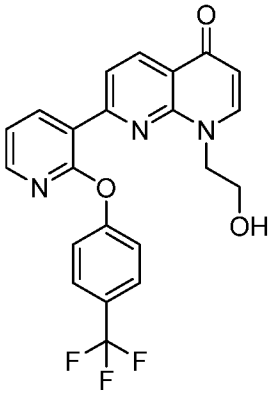
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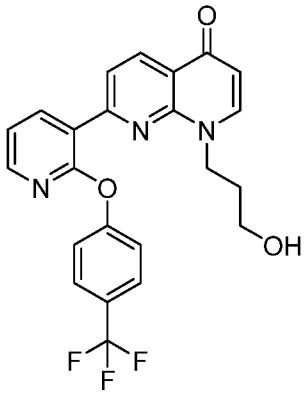
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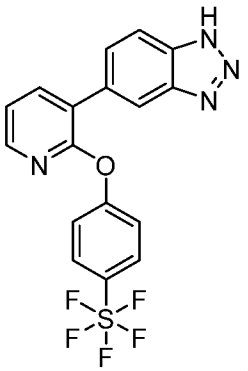
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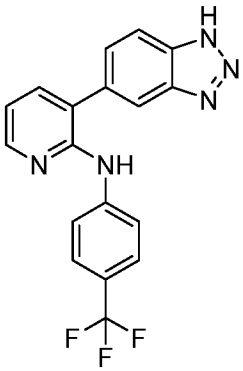
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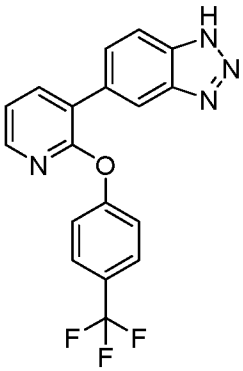
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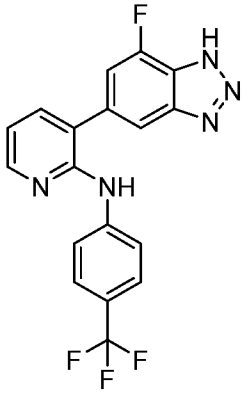
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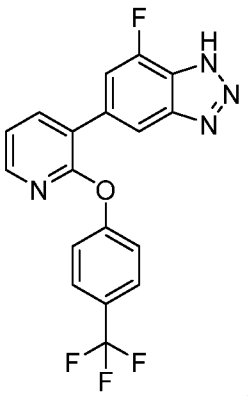
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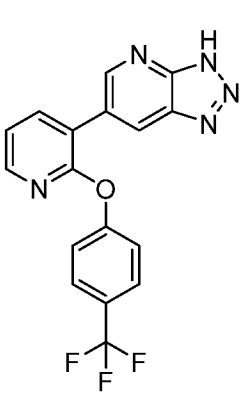
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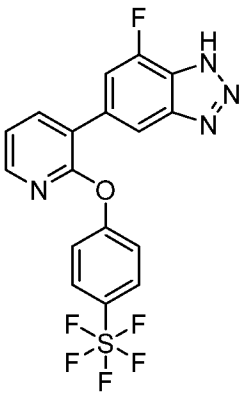
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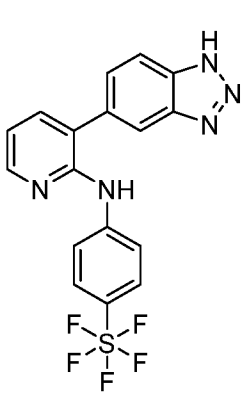
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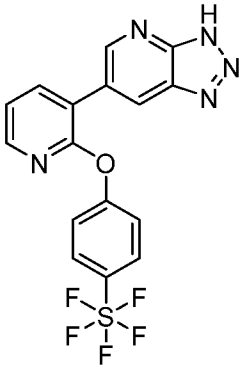
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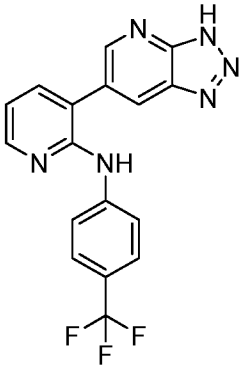
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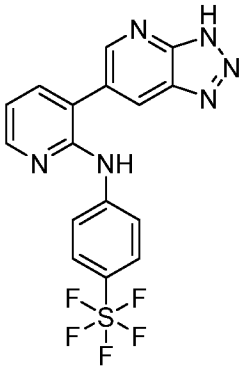
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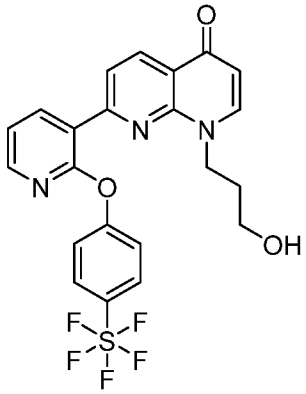
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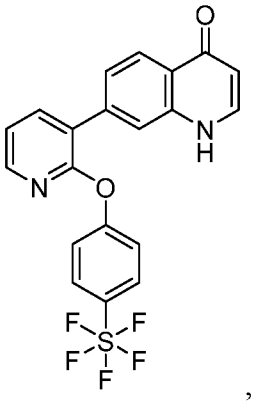
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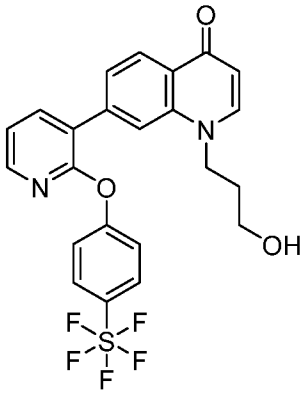
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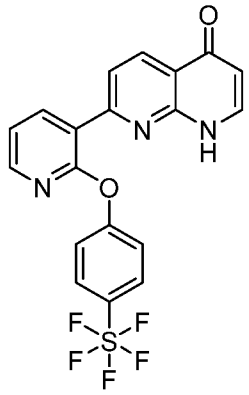
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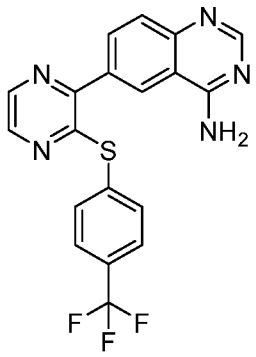
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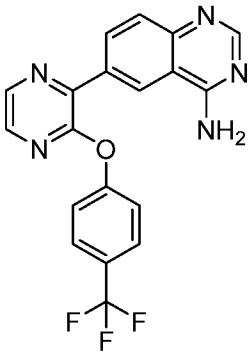
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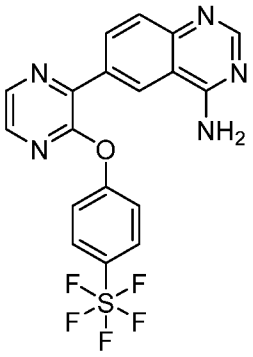
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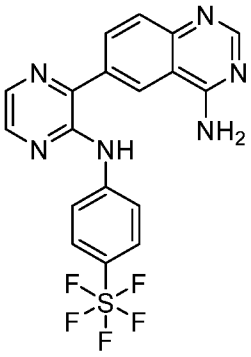
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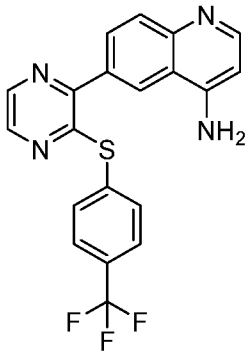
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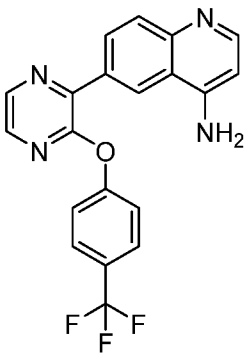
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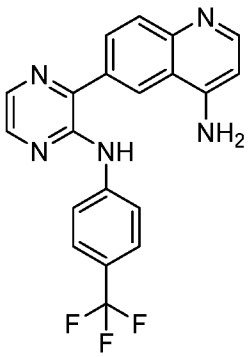
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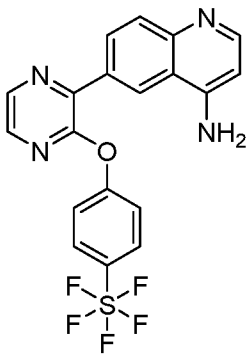
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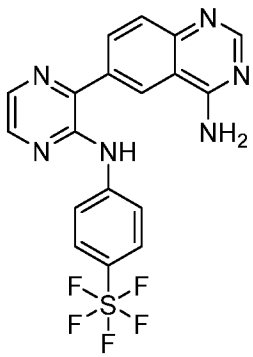
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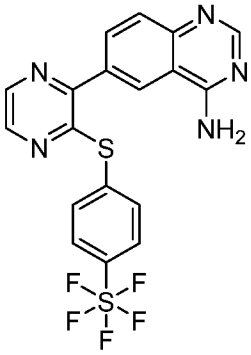
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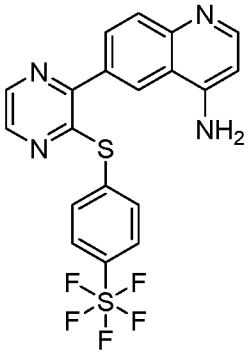
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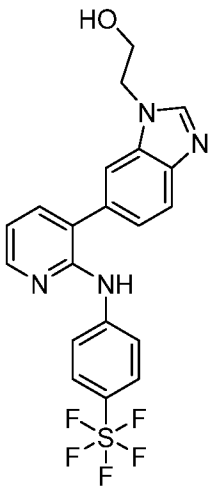
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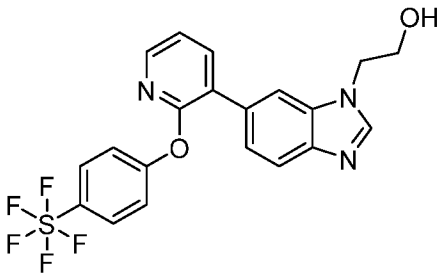
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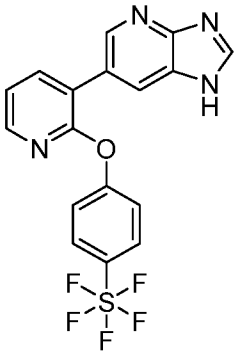
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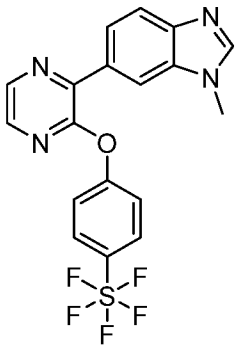
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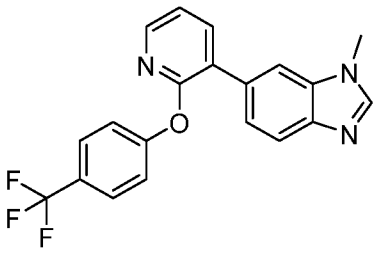
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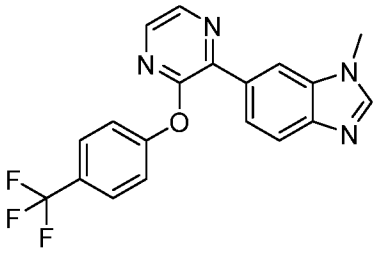
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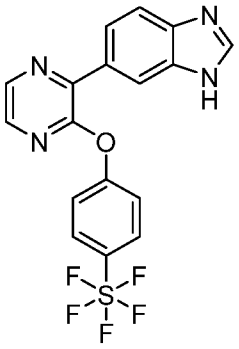
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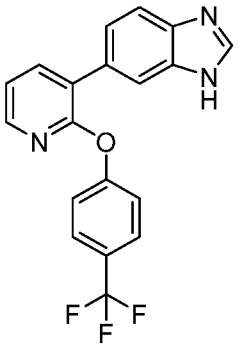
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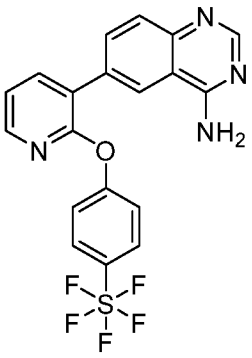
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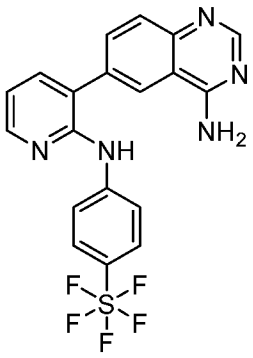
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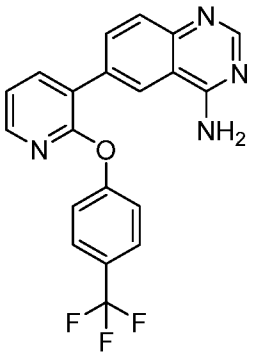
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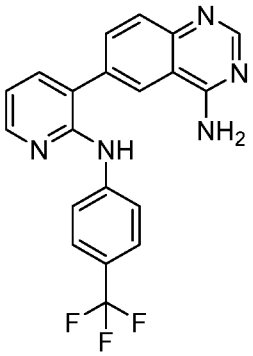
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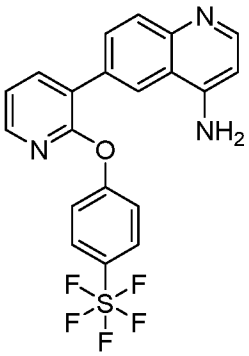
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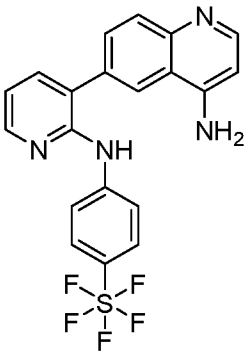
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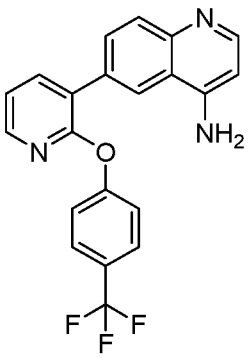
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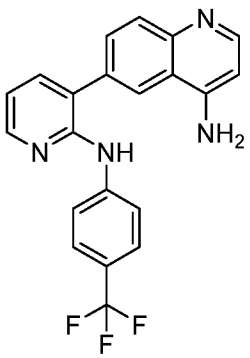
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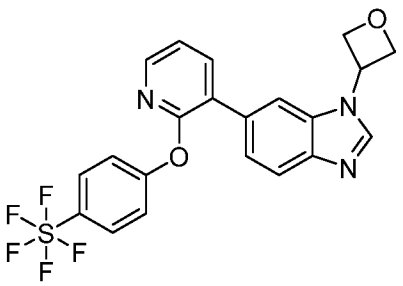
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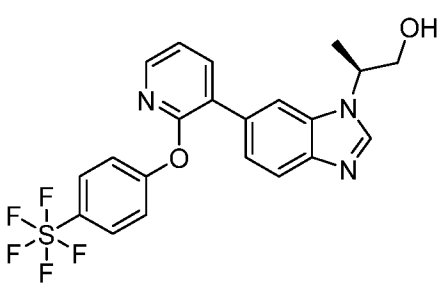
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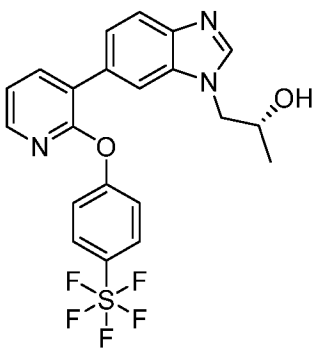
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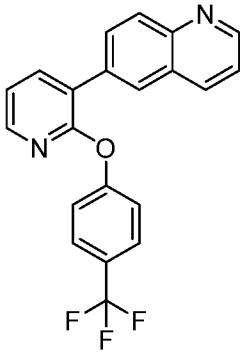
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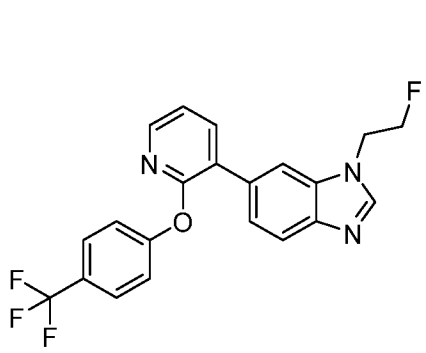
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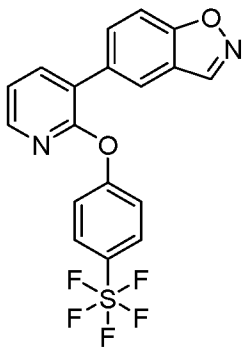
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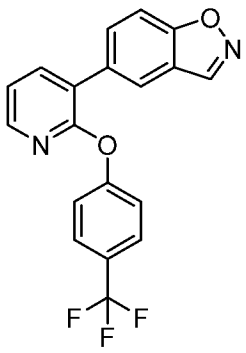
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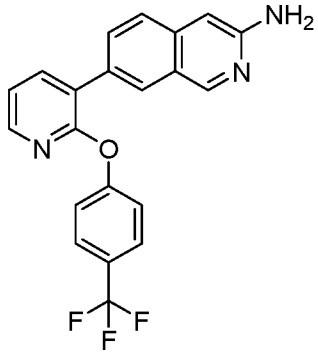
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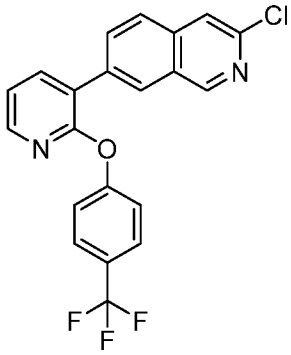
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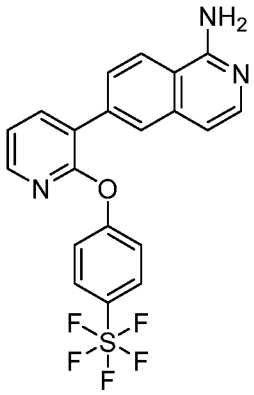
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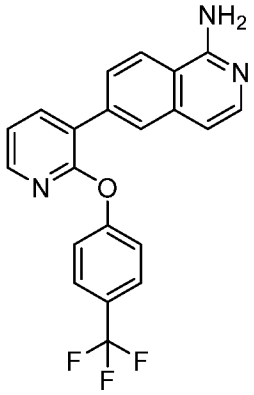
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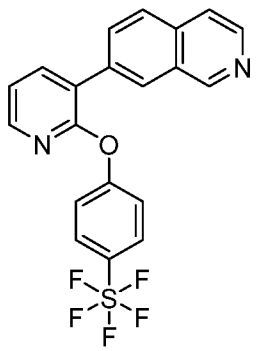
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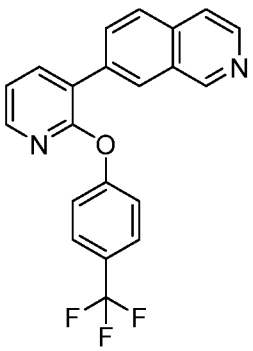
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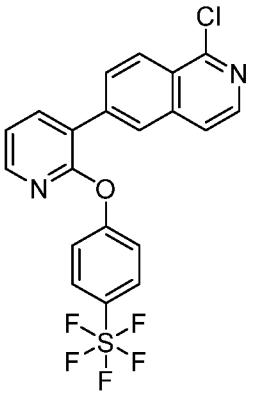
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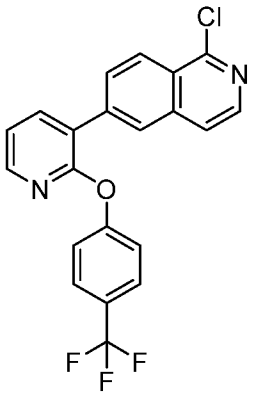
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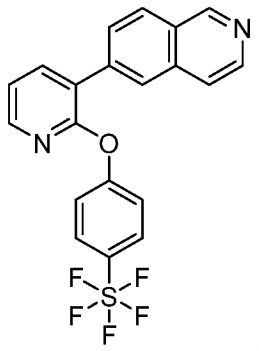
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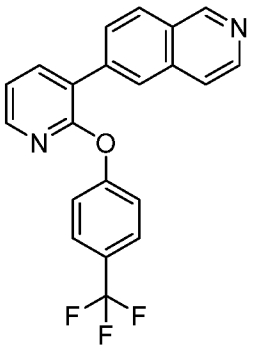
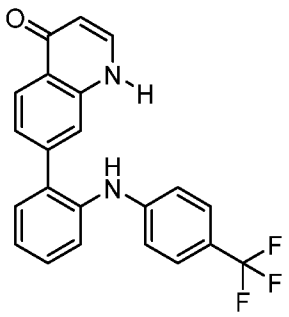
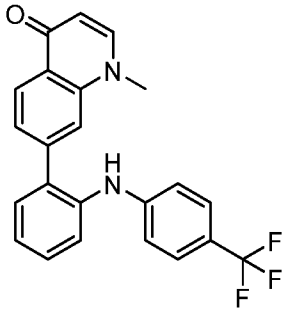
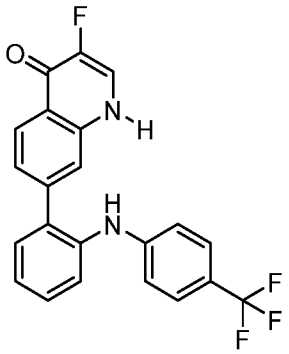
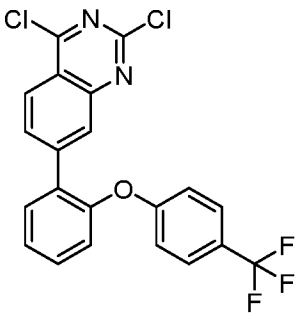
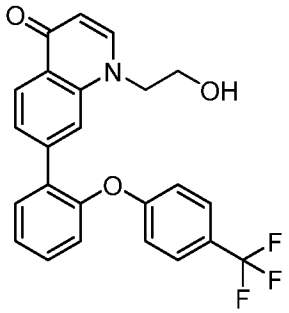
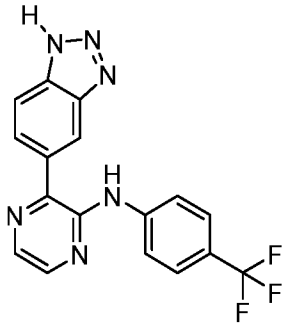
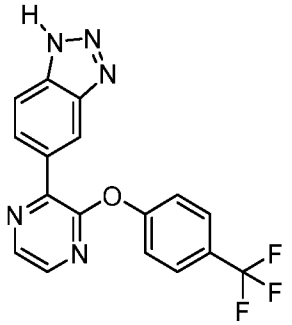
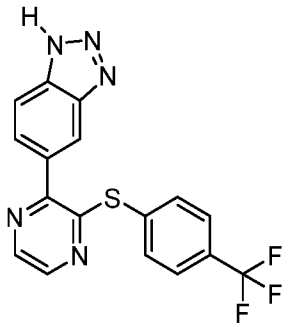
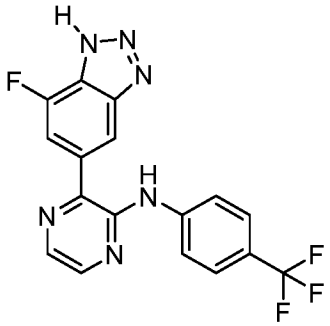
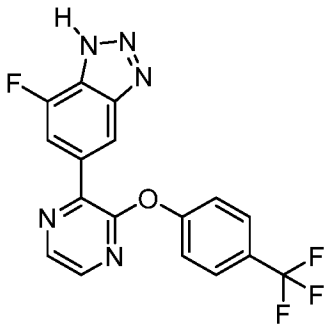

, and .

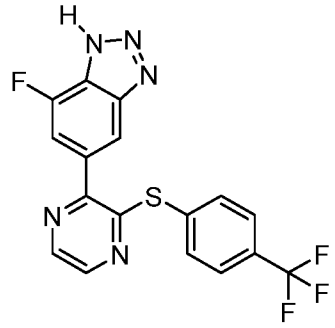
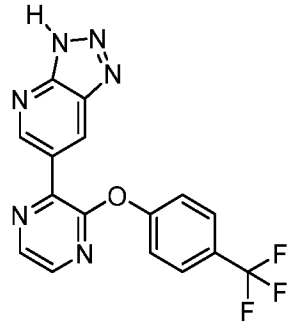
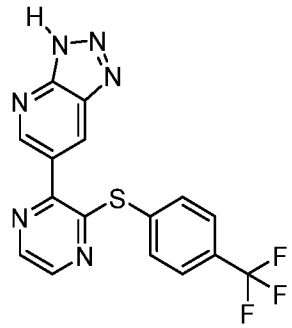
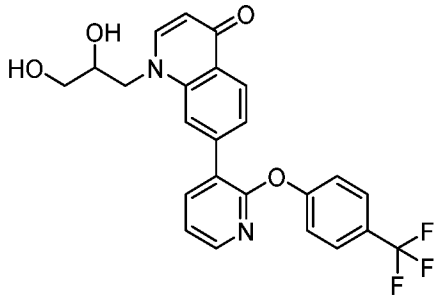
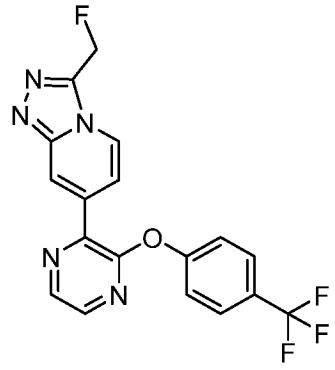
[00117] In another aspect, the present disclosure provides a compound or pharmaceutically acceptable salt thereof, wherein the compound is a compound from Table 1.

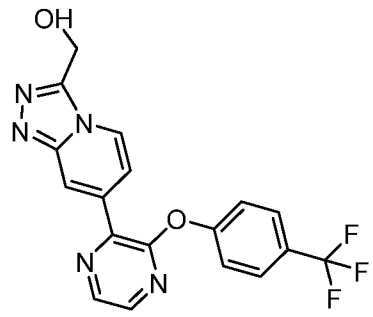
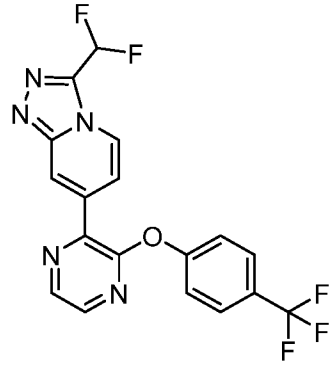
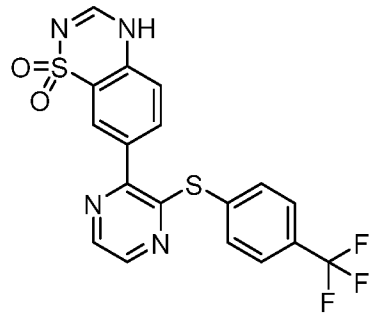
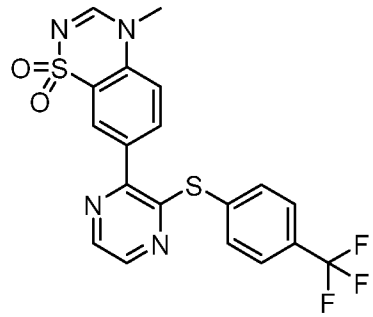
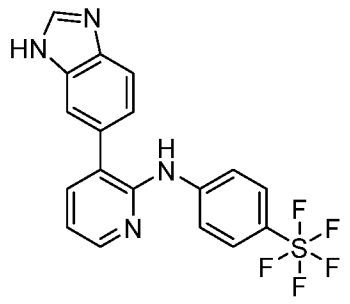
TABLE 1

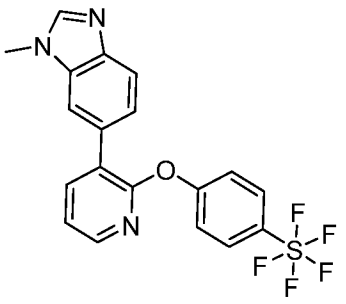
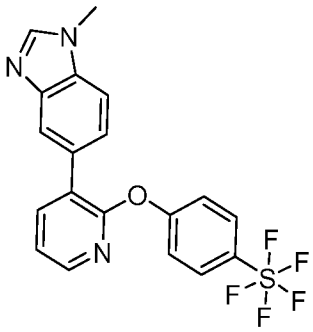
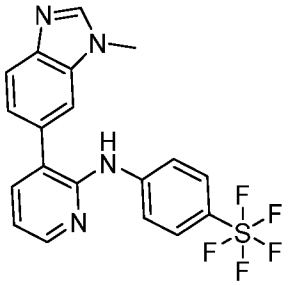
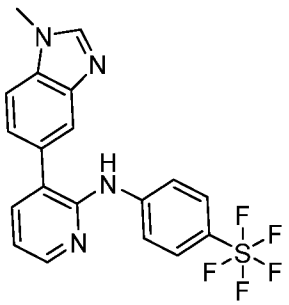
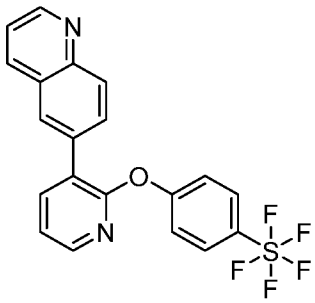
Compound #	Structure	Name

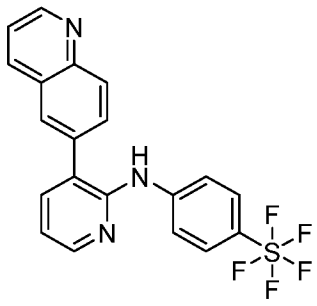
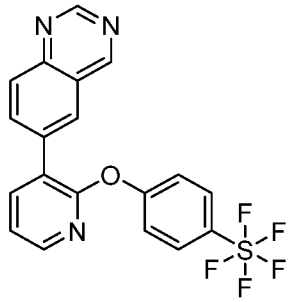
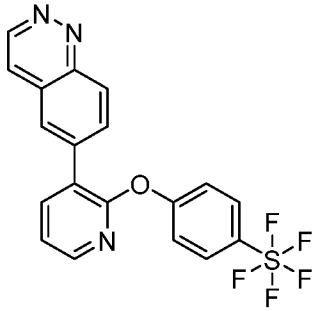
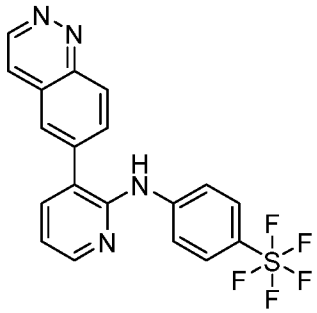
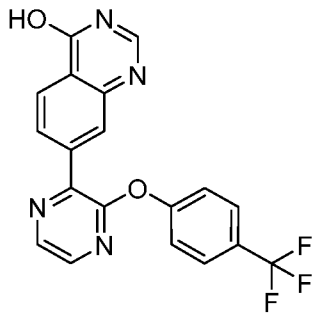
1		7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one
2		1-methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one
3		3-fluoro-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one
4		2,4-dichloro-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinazoline
5		1-(2-hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one

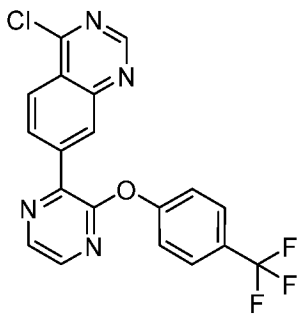
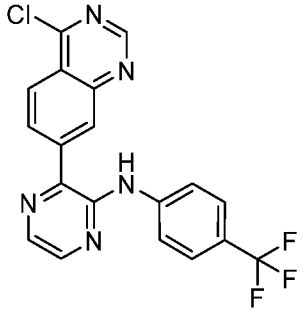
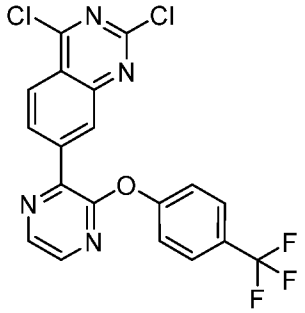
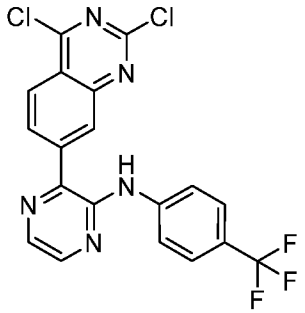
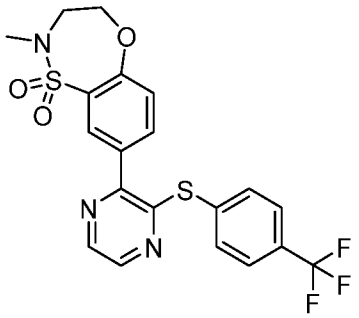
6		3-(1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
7		5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole
8		5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole
9		3-(7-fluoro-1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
10		7-fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole

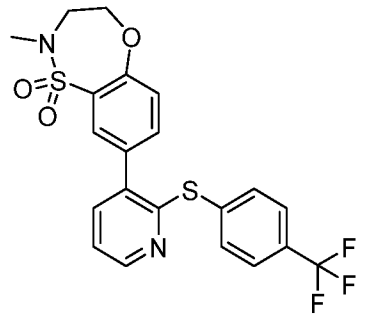
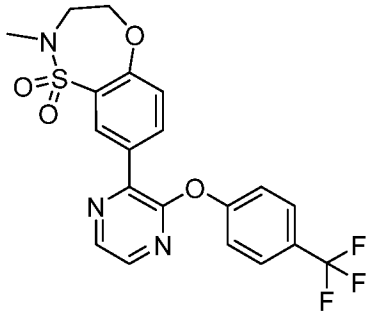
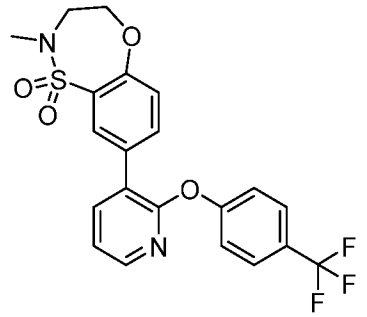
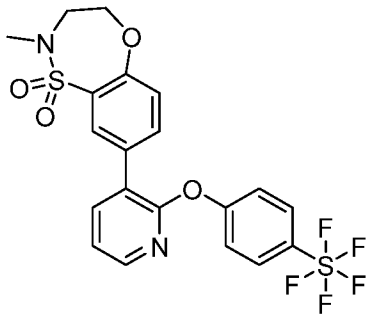
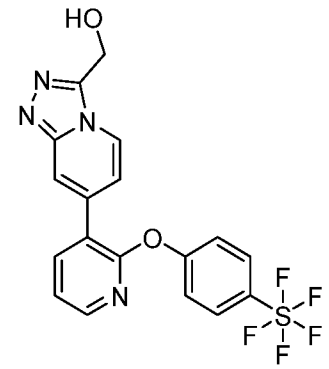
11		7-fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole
12		6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine
13		6-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine
14		1-(2,3-dihydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one
15		3-(fluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine

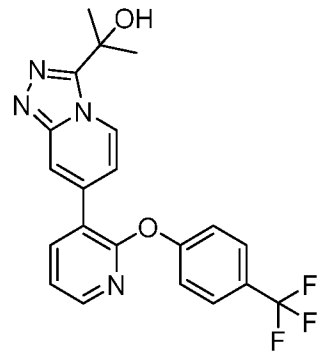
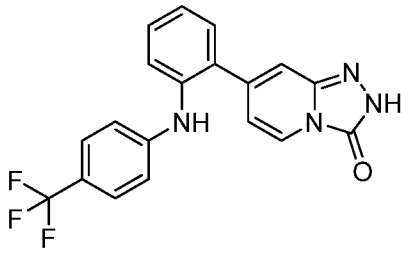
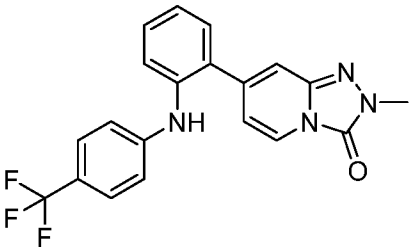
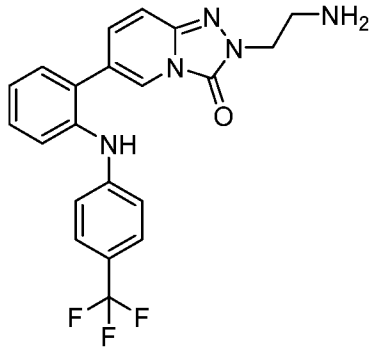
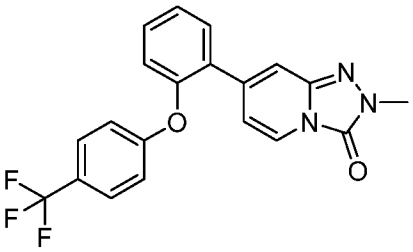
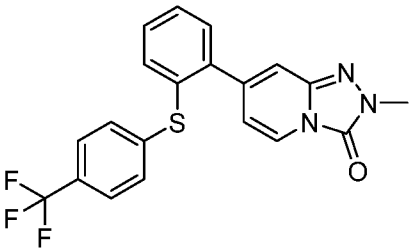
15A		(7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol
16		3-(difluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine
17		7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide
18		4-methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide
19		3-(1H-benzo[d]imidazol-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine

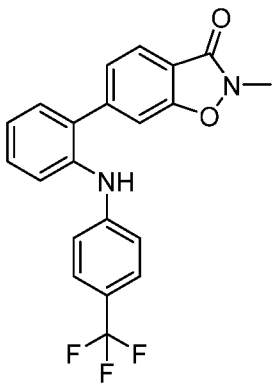
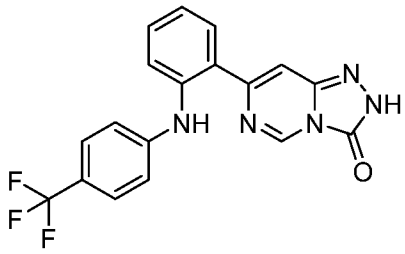
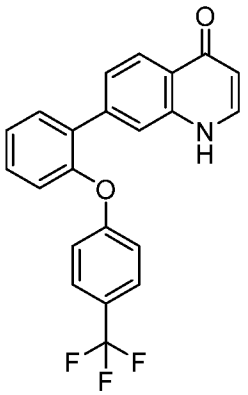
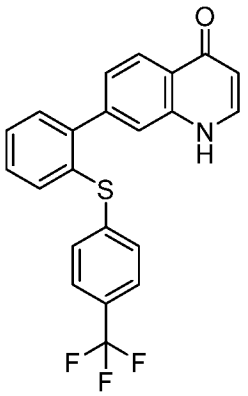
20		1-methyl-6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole
20a		1-methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole
21		3-(1-methyl-1H-benzo[d]imidazol-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine
21a		3-(1-methyl-1H-benzo[d]imidazol-5-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine
22		6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinoline

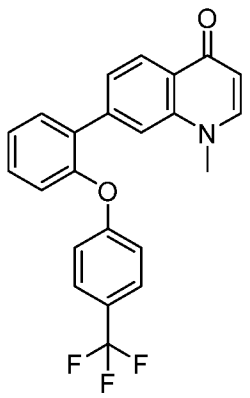
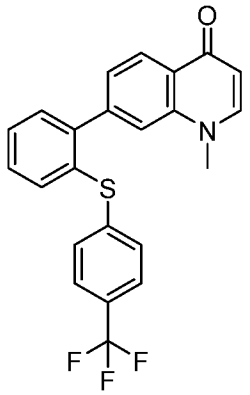
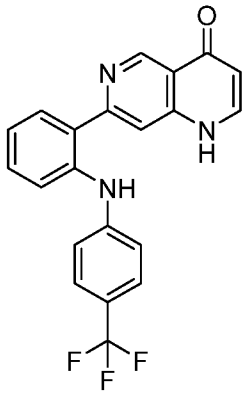
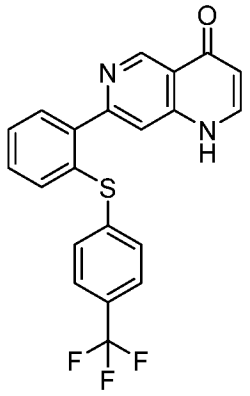
23		N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)-3-(quinolin-6-yl)pyridin-2-amine
24		6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinazoline
25		6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)cinnoline
26		3-(cinnolin-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine
27		7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-ol

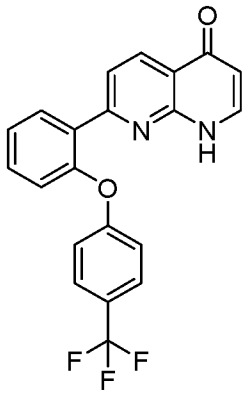
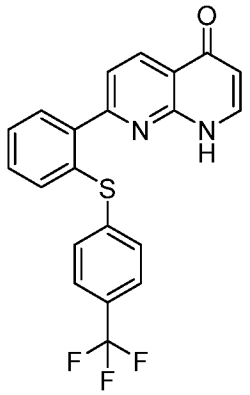
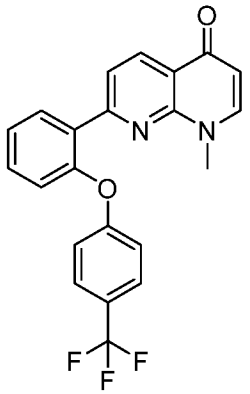
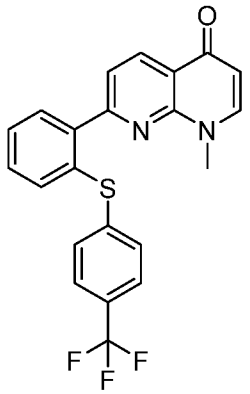
28		4-chloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline
29		3-(4-chloroquinazolin-7-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
30		2,4-dichloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline
31		3-(2,4-dichloroquinazolin-7-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine
32		2-methyl-8-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

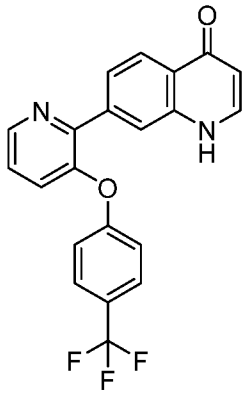
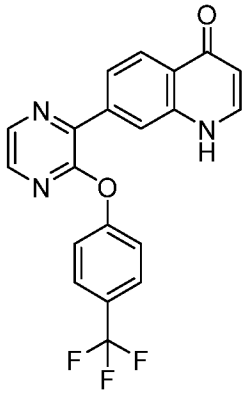
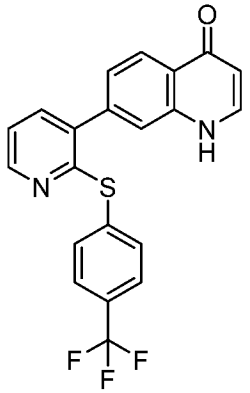
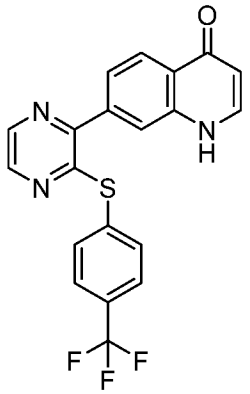
33		2-methyl-8-(2-((4-(trifluoromethyl)phenyl)thio)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide
34		2-methyl-8-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide
35		2-methyl-8-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide
36		2-methyl-8-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide
37		(7-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol

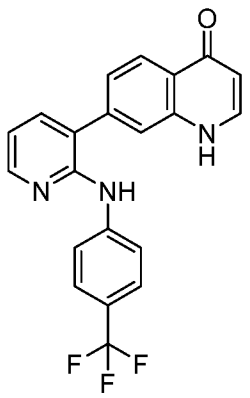
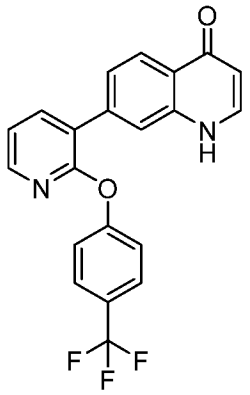
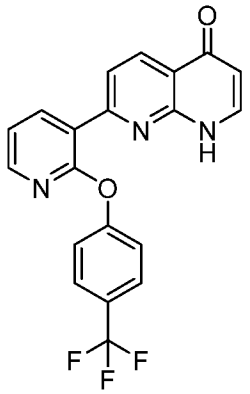
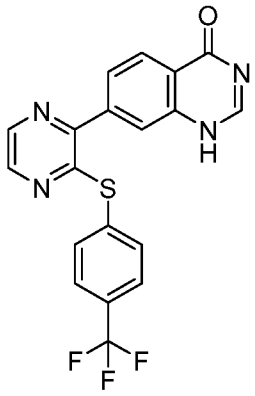
38		2-(7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-ol
39		7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
40		2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
41		2-(2-Aminoethyl)-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one
42		2-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one
43		2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one

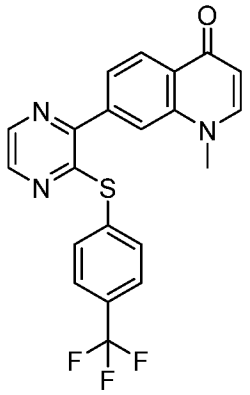
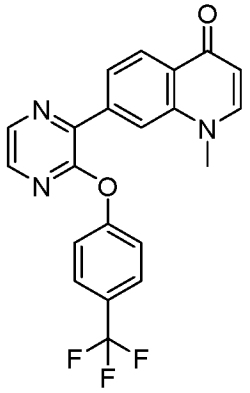
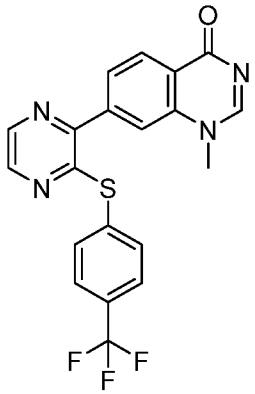
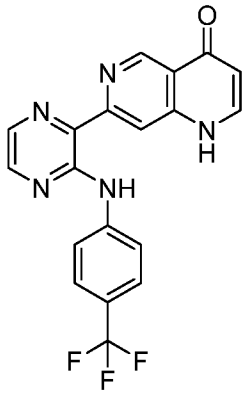
44		2-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)benzo[d]isoxazol-3(2*H*)-one
45		7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-*c*]pyrimidin-3(2*H*)-one
46		7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one
47		7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one

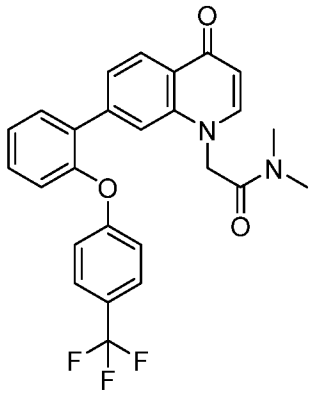
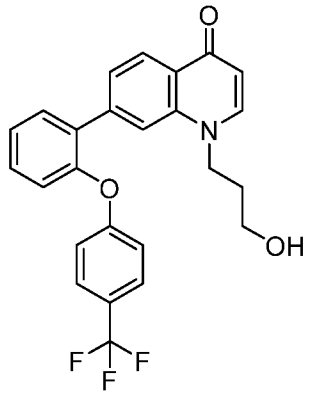
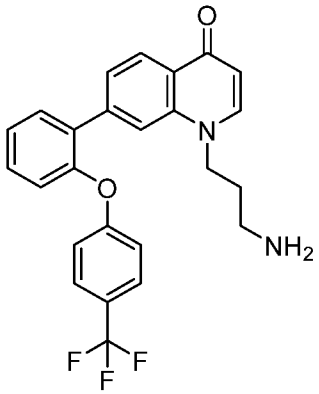
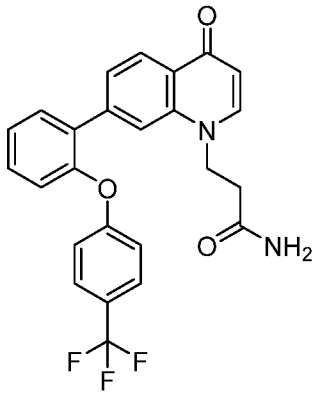
48		1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one
49		1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one
50		7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-1,6-naphthyridin-4(1*H*)-one
51		7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)-1,6-naphthyridin-4(1*H*)-one

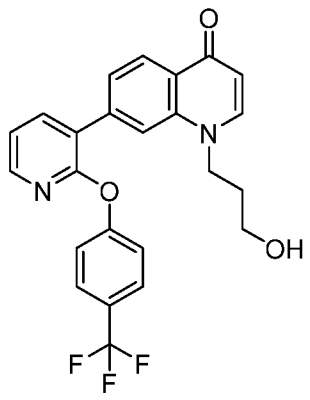
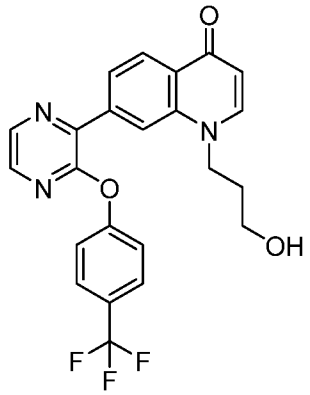
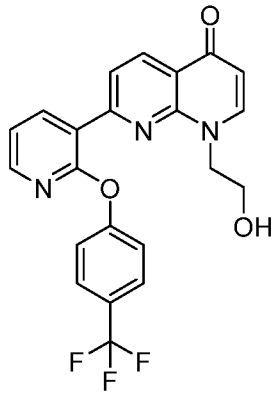
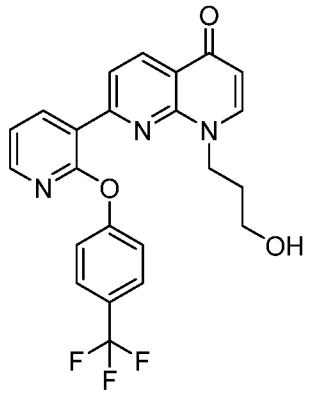
52		7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one
53		7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one
54		1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one
55		1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one

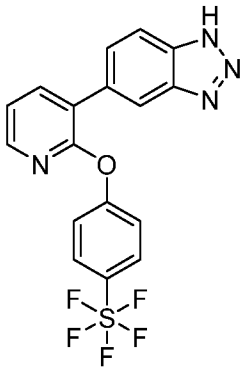
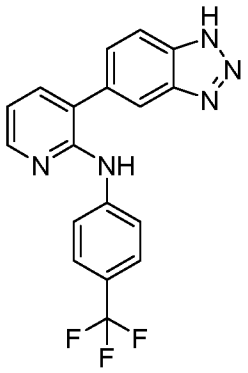
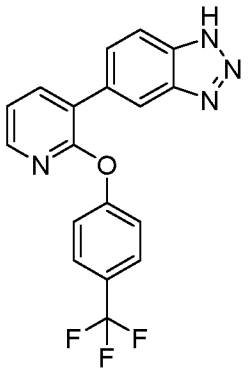
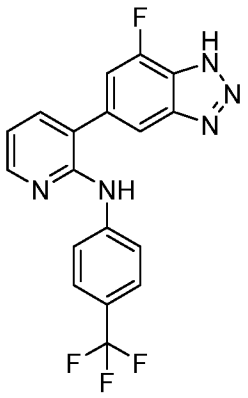
56		7-(3-(4-(Trifluoromethyl)phenoxy)pyridin-2-yl)quinolin-4(1H)-one
57		7-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one
58		7-(2-((4-(Trifluoromethyl)phenyl)thio)pyridin-3-yl)quinolin-4(1H)-one
59		7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one

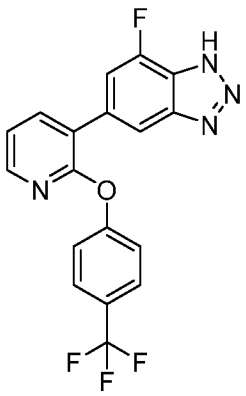
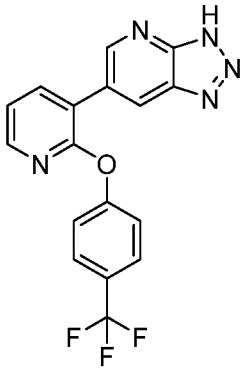
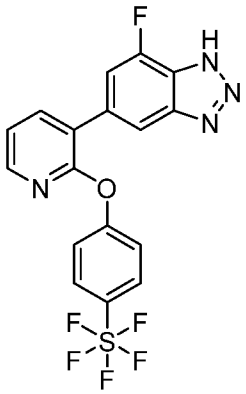
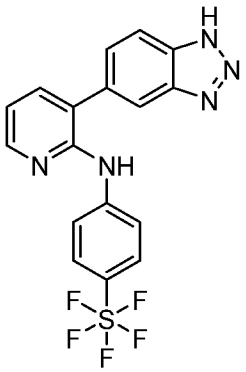
60		7-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4(1H)-one
61		7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one
62		7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one
63		7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one

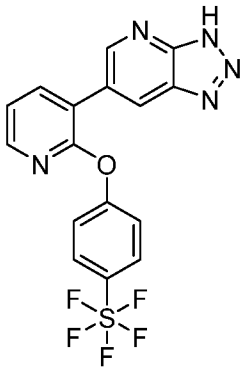
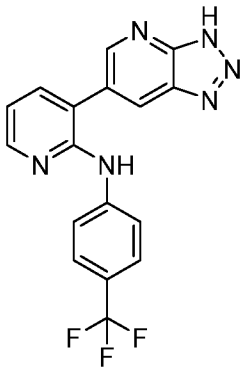
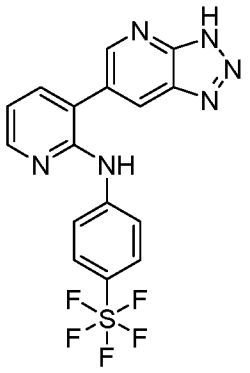
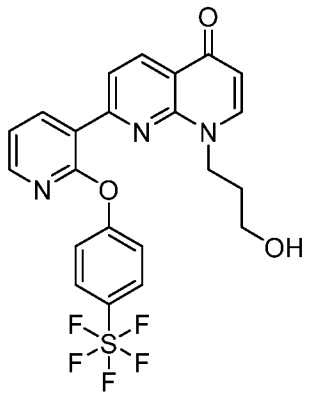
64		1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one
65		1-Methyl-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one
66		1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one
67		7-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)-1,6-naphthyridin-4(1H)-one

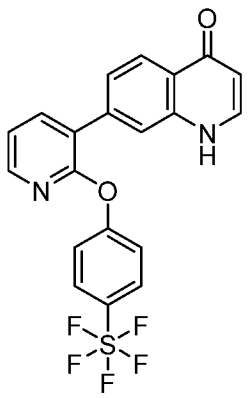
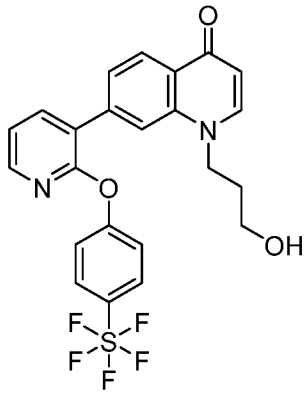
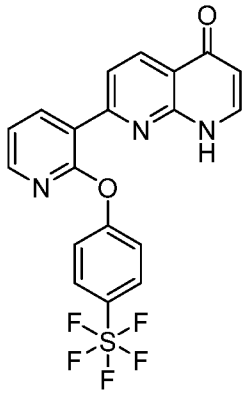
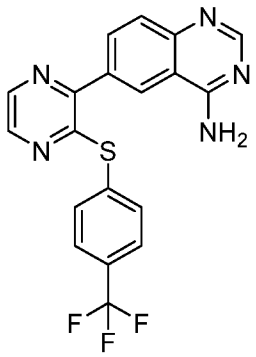
68		*N*,*N*-Dimethyl-2-(4-oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)acetamide
69		1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one
70		1-(3-Aminopropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one
71		3-(4-Oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)propanamide

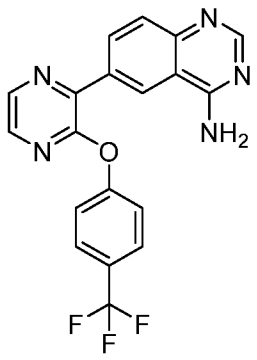
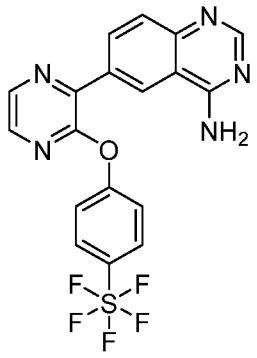
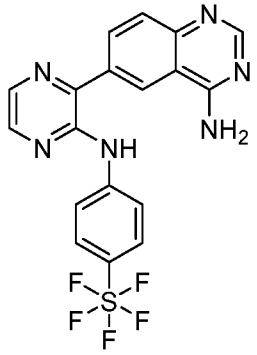
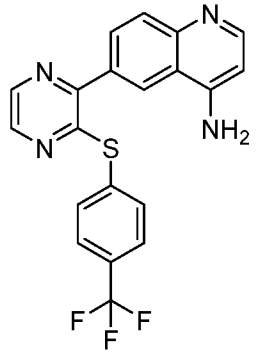
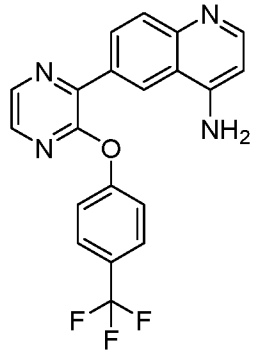
72		1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one
73		1-(3-Hydroxypropyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one
74		1-(2-Hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one
75		1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one

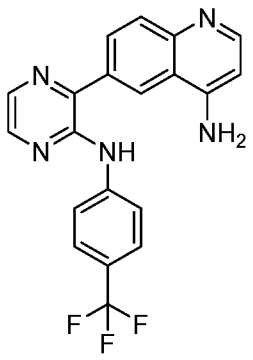
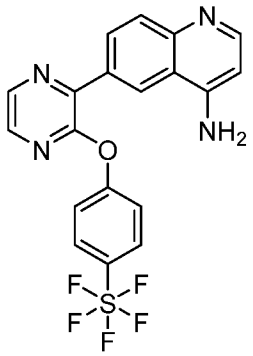
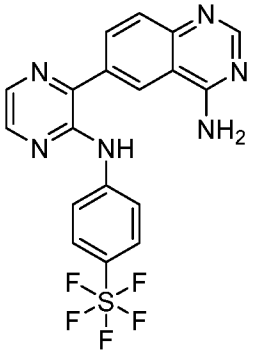
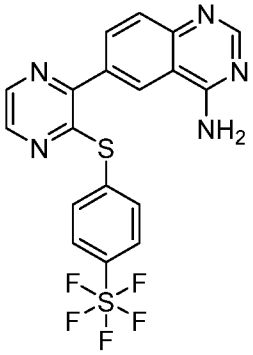
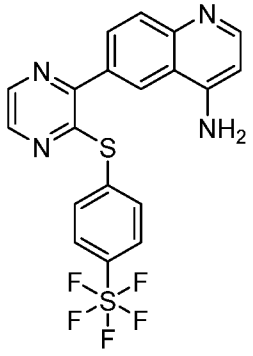
76		5-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole
77		3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine
78		5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole
79		3-(7-Fluoro-1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine

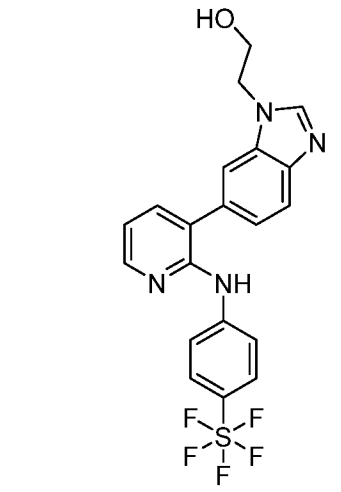
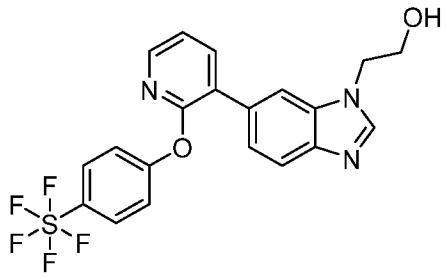
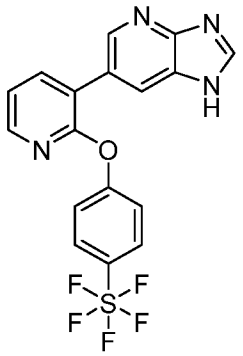
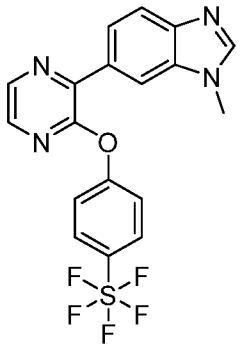
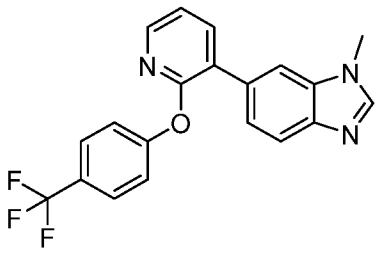
80		7-Fluoro-5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole
81		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine
82		7-Fluoro-5-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole
83		3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine

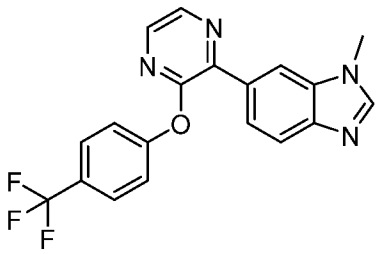
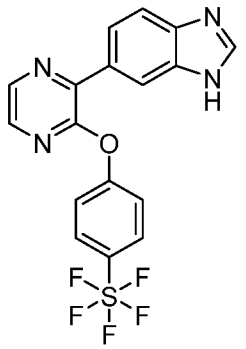
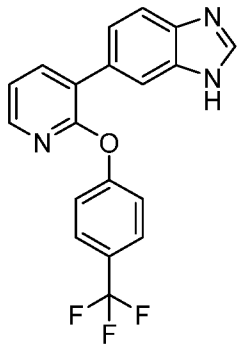
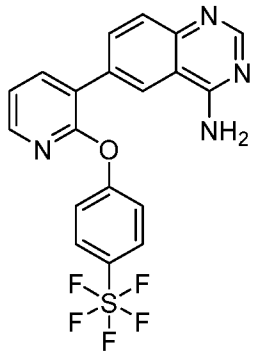
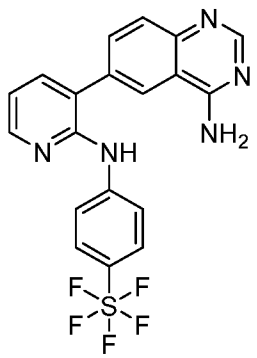
84		6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine
85		3-(3H-[1,2,3]Triazolo[4,5-b]pyridin-6-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine
86		6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine
87		1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one

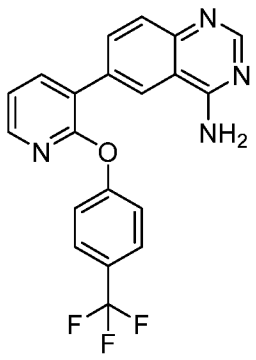
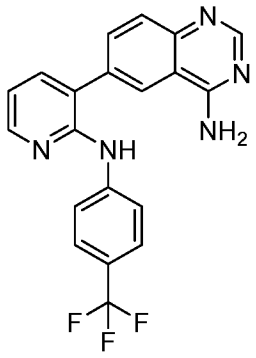
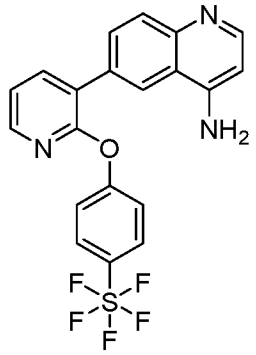
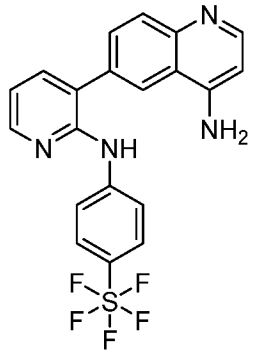
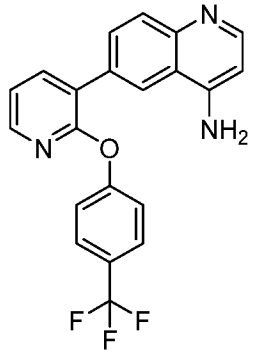
88		7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one
89		1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one
90		7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one
91		6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine

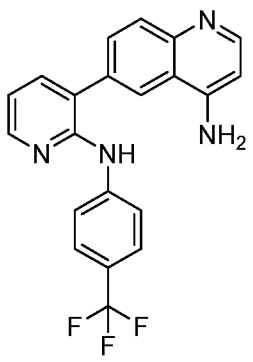
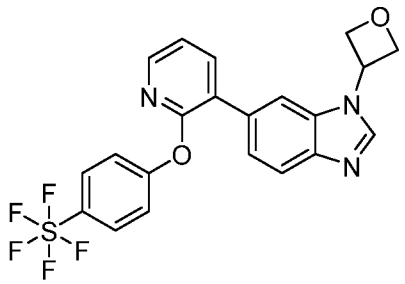
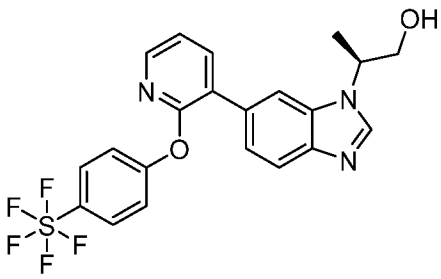
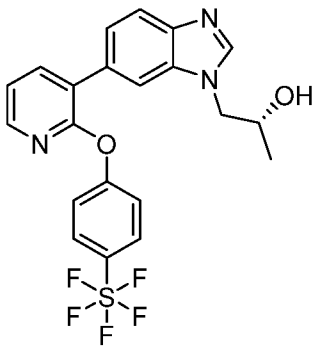
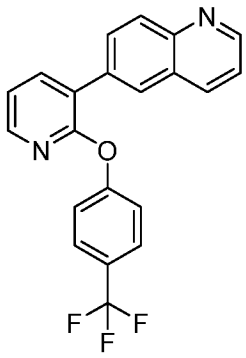
92		6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine
93		6-(3-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine
94		6-(3-((4-(pentafluoro- λ6-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinazolin-4-amine
95		6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4-amine
96		6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4-amine

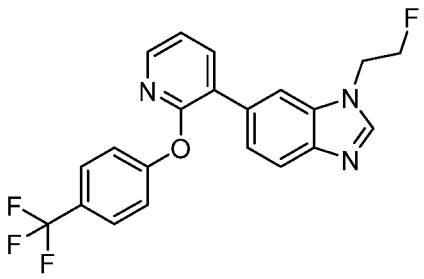
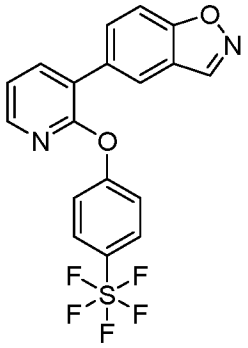
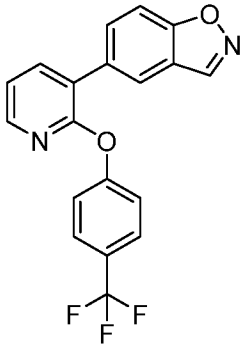
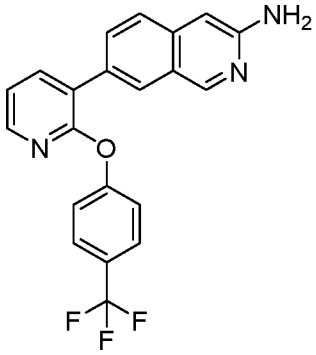
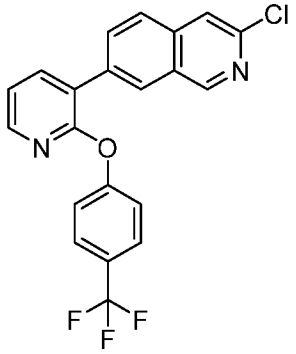
97		6-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine
98		6-(3-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyrazin-2-yl)quinolin-4-amine
99		6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine
100		6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine
101		6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinolin-4-amine

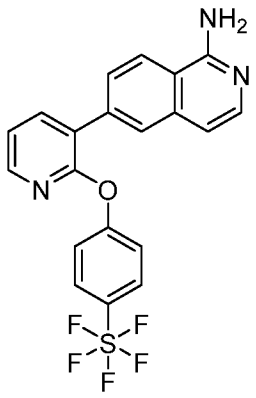
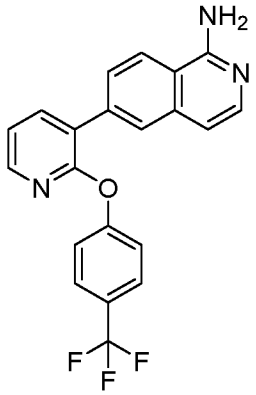
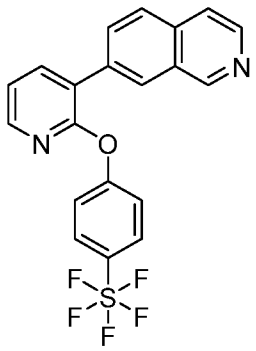
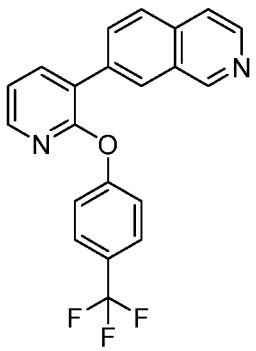
102		3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine
103		2-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-ol
104		6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-imidazo[4,5-b]pyridine
105		1-Methyl-6-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole
106		1-Methyl-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole

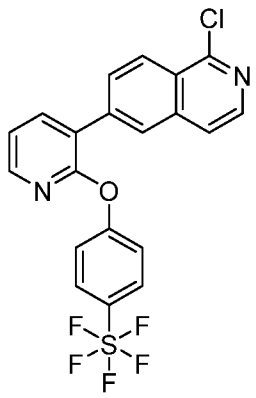
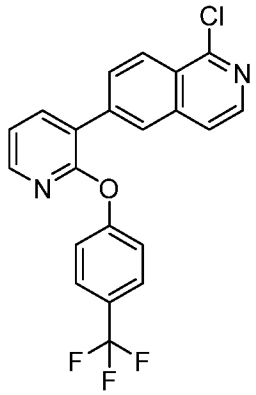
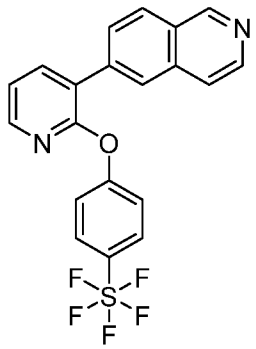
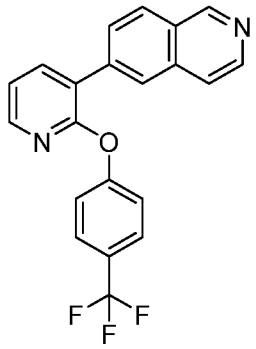
107		1-Methyl-6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole
108		6-(3-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole
109		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole
110		6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinazolin-4-amine
111		6-(2-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine

112		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinazolin-4-amine
113		6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine
114		6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4-amine
115		6-(2-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine
116		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4-amine

117		6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine
118		1-(Oxetan-3-yl)-6-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole
119		(S)-2-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propan-1-ol
120		(S)-1-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propan-2-ol
121		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinoline

122		1-(2-Fluoroethyl)-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole
123		5-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole
124		5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole
125		7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-3-amine
126		3-Chloro-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline

127		6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine
128		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine
129		7-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline
130		7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline

131		1-Chloro-6-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline
132		1-Chloro-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline
133		6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline
134		6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline

[00118] In some embodiments, provided is a pharmaceutically acceptable salt or solvate thereof of a compound described in Table 1.

Further Forms of Compounds

Isomers

[00119] Furthermore, in some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds presented herein include all cis, trans, syn, anti, entgegen (*E*), and zusammen (*Z*) isomers as well as the corresponding mixtures thereof. In some situations, compounds exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein. In some situations, the compounds described herein possess one or more chiral centers and each center exists in the R configuration, or S configuration. The compounds described herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, disclosed herein are dissociable complexes (e.g., crystalline diastereomeric salts). In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that does not result in racemization.

Labeled compounds

[00120] In some embodiments, the compounds described herein exist in their isotopically-labeled forms. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such isotopically-labeled compounds as pharmaceutical compositions. Thus, in some embodiments, the compounds disclosed herein include isotopically-labeled compounds, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. In some embodiments, examples of isotopes that are incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds described herein, and the metabolites, pharmaceutically acceptable salts, esters, prodrugs, solvates,

hydrates, or derivatives thereof which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this disclosure. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i. e., ^{3}H and carbon-14, i. e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavy isotopes such as deuterium, *i.e.*, ^{2}H, produces certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. In some embodiments, the isotopically labeled compounds, pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof is prepared by any suitable method.

[00121] In some embodiments, the compounds described herein are labeled by other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

Pharmaceutically acceptable salts

[00122] In some embodiments, the compounds described herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[00123] In some embodiments, the compounds described herein possess acidic or basic groups and therefore react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds of the disclosure, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

Solvates

[00124] In some embodiments, the compounds described herein exist as solvates. The disclosure provides for methods of treating diseases by administering such solvates. The disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[00125] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and, in some embodiments, are formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of the compounds described herein are conveniently prepared or formed during the processes described

herein. By way of example only, hydrates of the compounds described herein are conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents including, but not limited to, dioxane, tetrahydrofuran, or methanol. In some embodiments, the compounds provided herein exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Prodrugs

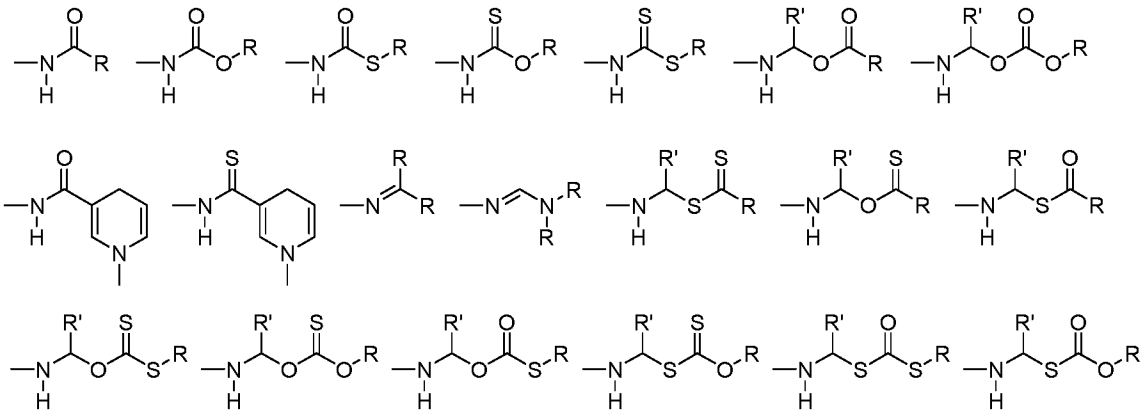
[00126] In some embodiments, the compounds described herein exist in prodrug form. The disclosure provides for methods of treating diseases by administering such prodrugs. The disclosure further provides for methods of treating diseases by administering such prodrugs as pharmaceutical compositions.

[00127] In some embodiments, prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e. g., two, three, or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of compounds of the present disclosure. The amino acid residues include, but are not limited to, the 20 naturally occurring amino acids and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvaline, beta-alanine, gamma-aminobutyric acid, cirtulline, homocysteine, homoserine, ornithine, and methionine sulfone. In other embodiments, prodrugs include compounds wherein a nucleic acid residue, or an oligonucleotide of two or more (e. g., two, three or four) nucleic acid residues is covalently joined to a compound of the present disclosure.

[00128] Pharmaceutically acceptable prodrugs of the compounds described herein also include, but are not limited to, esters, carbonates, thiocarbonates, N-acyl derivatives, N-acyloxyalkyl derivatives, quaternary derivatives of tertiary amines, N-Mannich bases, Schiff bases, amino acid conjugates, metal salts, and sulfonate esters. In some embodiments, compounds having free amino, amido, hydroxy, or carboxylic groups are converted into prodrugs. For instance, free carboxyl groups are derivatized as amides or alkyl esters. In certain instances, all of these prodrug moieties incorporate groups including, but not limited to, ether, amine, and carboxylic acid functionalities.

[00129] Hydroxy prodrugs include esters such as, though not limited to, acyloxyalkyl (e.g., acyloxymethyl, acyloxyethyl) esters, alkoxycarbonyloxyalkyl esters, alkyl esters, aryl esters, sulfonate esters, sulfate esters and disulfide containing esters, ethers, amides, carbamates, hemisuccinates, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in *Advanced Drug Delivery Reviews* **1996**, *19*, 115.

[00130] Amine derived prodrugs include, but are not limited to, the following groups and combinations of groups:



as well as sulfonamides and phosphonamides.

[00131] In certain instances, sites on any aromatic ring portions are susceptible to various metabolic reactions, therefore incorporation of appropriate substituents on the aromatic ring structures reduce, minimize, or eliminate this metabolic pathway.

Metabolites

[00132] In some embodiments, compounds described herein are susceptible to various metabolic reactions. Therefore, in some embodiments, incorporation of appropriate substituents into the structure will reduce, minimize, or eliminate a metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of an aromatic ring to metabolic reactions is, by way of example only, a halogen or an alkyl group.

[00133] In additional or further embodiments, the compounds described herein are metabolized upon administration to an organism in need to produce a metabolite that is then used to produce a desired effect, including a desired therapeutic effect.

Preparation of the Compounds

[00134] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis

(Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[00135] Methods known to one of ordinary skill in the art are identified through various reference books and databases. Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[00136] In some instances, specific and analogous reactants are identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., is contacted for more details). Chemicals that are

known but not commercially available in catalogs are prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

[00137] In some embodiments, the compounds disclosed herein are prepared as described in the Examples section.

Pharmaceutical Compositions

[00138] In certain embodiments, the compound as described herein is administered as a pure chemical. In other embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)), the disclosure of which is hereby incorporated herein by reference in its entirety.

[00139] Accordingly, provided herein is a pharmaceutical composition comprising at least one compound described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, solvate, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject) of the composition.

[00140] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (III-a), (III-b), (III-c), (IV), (V), or (VI), or a pharmaceutically acceptable salt or solvate thereof.

[00141] Another embodiment provides a pharmaceutical composition consisting essentially of a pharmaceutically acceptable carrier and a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (III-a), (III-b), (III-c), (IV), (V), or (VI), or a pharmaceutically acceptable salt or solvate thereof.

[00142] In certain embodiments, the compound as described herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as contaminating intermediates or by-products that are created, for example, in one or more of the steps of a synthesis method.

[00143] These formulations include those suitable for oral, rectal, topical, buccal, parenteral (*e.g.*, subcutaneous, intramuscular, intradermal, or intravenous), rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions are formulated as a unit dose, and/or are formulated for oral or subcutaneous administration.

[00144] In some instances, exemplary pharmaceutical compositions are used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which includes one or more of the disclosed compounds, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. In some embodiments, the active ingredient is compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00145] For preparing solid compositions such as tablets in some instances, the principal active ingredient is mixed with a pharmaceutical carrier, *e.g.*, conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, or gums, and other pharmaceutical diluents, *e.g.*, water, to form a solid preformulation composition containing a homogeneous mixture of a disclosed compound or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition is readily subdivided into equally effective unit dosage forms such as tablets, pills, and capsules.

[00146] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc,

calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions also comprise buffering agents in some embodiments. Solid compositions of a similar type are also employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00147] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms contain optionally inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers.

[00148] Suspensions, in addition to the subject composition, optionally contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00149] In some embodiments, the doses of the composition comprising at least one compound as described herein differ, depending upon the patient's (*e.g.,* human) condition, that is, stage of the disease, general health status, age, and other factors that a person skilled in the medical art will use to determine dose.

[00150] In some instances, pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented) as determined by persons skilled in the medical arts. An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.,* an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. In some embodiments, the optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00151] In some embodiments, oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

The Hippo Signaling Network

[00152] The Hippo signaling network (also known as the Salvador/Warts/Hippo (SWH) pathway) is a master regulator of cell proliferation, death, and differentiation. In some embodiments, the main function of the Hippo signaling pathway is to regulate negatively the

transcriptional co-activators Yes-associated protein (YAP) and its paralogue, the transcriptional co-activator with PDZ-binding motif (TAZ; also known as WWTR1). The Hippo kinase cascade phosphorylates and inhibits YAP/TAZ by promoting its cytoplasmic retention and degradation, thereby inhibiting the growth promoting function regulated under the YAP/TAZ control. In an un-phosphorylated/de-phosphorylated state, YAP, also known as YAP1 or YAP65, together with TAZ, are transported into the nucleus where they interact with TEtOAcD family of transcription factors to upregulate genes that promote proliferation and migration, and inhibit apoptosis. In some instances, unregulated upregulation of these genes involved in proliferation, migration, and anti-apoptosis leads to development of cancer. In some instances, overexpression of YAP/TAZ is associated with cancer.

[00153] Additional core members of the Hippo signaling pathway comprise the serine/threonine kinases MST1/2 (homologues of *Hippo/Hpo* in Drosophila), Lats1/2 (homologues of *Warts/Wts*), and their adaptor proteins Sav1 (homologue of *Salvador/Sav*) and Mob (MOBKL1A and MOBKL1B; homologues of *Mats*), respectively. In general, MST1/2 kinase complexes with the scaffold protein Sav1, which in turn phosphorylates and activates Lats1/2 kinase. Lats1/2 is also activated by the scaffold protein Mob. The activated Lats1/2 then phosphorylates and inactivates YAP or its paralog TAZ. The phosphorylation of YAP/TAZ leads to their nuclear export, retention within the cytoplasm, and degradation by the ubiquitin proteasome system.

[00154] In some instances, Lats1/2 phosphorylates YAP at the [HXRXXS] consensus motifs. YAP comprises five [HXRXXS] consensus motifs, wherein X denotes any amino acid residue. In some instances, Lats1/2 phosphorylates YAP at one or more of the consensus motifs. In some instances, Lats1/2 phosphorylates YAP at all five of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S127 amino acid position. The phosphorylation of YAP S127 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of YAP. Mutation of YAP at the S127 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00155] Additional phosphorylation occurs at the S381 amino acid position in YAP. Phosphorylation of YAP at the S381 position and on the corresponding site in TAZ primes both proteins for further phosphorylation events by CK1δ/ε in the degradation motif, which then signals for interaction with the β-TRCP E3 ubiquitin ligase, leading to polyubiquitination and degradation of YAP.

[00156] In some instances, Lats1/2 phosphorylates TAZ at the [HXRXXS] consensus motifs. TAZ comprises four [HXRXXS] consensus motifs, wherein X denotes any amino acid residues. In some instances, Lats1/2 phosphorylates TAZ at one or more of the consensus motifs. In some

instances, Lats1/2 phosphorylates TAZ at all four of the consensus motifs. In some instances, Lats1/2 phosphorylate at the S89 amino acid position. The phosphorylation of TAZ S89 promotes 14-3-3 protein binding and results in cytoplasmic sequestration of TAZ. Mutation of TAZ at the S89 position thereby disrupts its interaction with 14-3-3 and subsequently promotes nuclear translocation.

[00157] In some embodiments, phosphorylated YAP/TAZ accumulates in the cytoplasm, and undergoes $SCF^{\beta\text{-}TRCP}$-mediated ubiquitination and subsequent proteasomal degradation. In some instances, the Skp, Cullin, F-box containing complex (SCF complex) is a multi-protein E3 ubiquitin ligase complex that comprises a F-box family member protein (e.g., Cdc4), Skp1, a bridging protein, and RBX1, which contains a small RING Finger domain which interacts with E2-ubiquitin conjugating enzyme. In some cases, the F-box family comprises more than 40 members, in which exemplary members include F-box/WD repeat-containing protein 1A (FBXW1A, βTrCP1, Fbxw1, hsSlimb, plkappaBalpha-E3 receptor subunit) and S-phase kinase-associated proteins 2 (SKP2). In some embodiments, the SCF complex (e.g., $SCF^{\beta TrCP1}$) interacts with an E1 ubiquitin-activating enzyme and an E2 ubiquitin-conjugating enzyme to catalyze the transfer of ubiquitin to the YAP/TAZ substrate. Exemplary E1 ubiquitin-activating enzymes include those encoded by the following genes: *UBA1, UBA2, UBA3, UBA5, UBA5, UBA7, ATG7, NAE1*, and *SAE1*. Exemplary E2 ubiquitin-conjugating enzymes include those encoded by the following genes: *UBE2A, UBE2B, UBE2C, UBE2D1, UBE2D2, UBE2D3, UBE2E1, UBE2E2, UBE2E3, UBE2F, UBE2G1, UBE2G2, UBE2H, UBE2I, UBE2J1, UBE2J2, UBE2K, UBE2L3, UBE2L6, UBE2M, UBE2N, UBE2O, UBE2Q1, UBE2Q2, UBE2R1, UBE2R2, UBE2S, UBE2T, UBE2U, UBE2V1, UBE2V2, UBE2Z, ATG2, BIRC5*, and *UFC1*. In some embodiments, the ubiquitinated YAP/TAZ further undergoes the degradation process through the 26S proteasome.

[00158] In some embodiments, the Hippo pathway is regulated upstream by several different families of regulators. In some instances, the Hippo pathway is regulated by the G-protein and its coupled receptors, the Crumbs complex, regulators upstream of the MST kinases, and the adherens junction.

YAP/TAZ Interaction with TEtOAcD

[00159] In some embodiments, un-phosphorylated and/or dephosphorylated YAP/TAZ accumulates in the nucleus. Within the nucleus, YAP/TAZ interacts with the TEtOAcD family of transcription factors (e.g., TEtOAcD1, TEtOAcD2, TEtOAcD3, or TEtOAcD4) to activate genes involved in anti-apoptosis and proliferation, such as for example *CTFG*, *Cyr61*, and *FGF1*.

[00160] In some embodiments, the compounds disclosed herein modulate the interaction between YAP/TAZ and TEtOAcD. In some embodiments, the compounds disclosed herein bind to TEtOAcD, YAP, or TAZ and prevent the interaction between YAP/TAZ and TEtOAcD.

YAP/TAZ regulation mediated by G-proteins/GPCRs

[00161] In some embodiments, the Hippo pathway is regulated by the G protein-coupled receptor (GPCR) and G protein (also known as guanine nucleotide-binding proteins) family of proteins. G proteins are molecular switches that transmit extracellular stimuli into the cell through GPCRs. In some instances, there are two classes of G proteins: monomeric small GTPases and heterotrimeric G protein complexes. In some instances, the latter class of complexes comprise of alpha (G_α), beta (G_β), and gamma (G_γ) subunits. In some cases, there are several classes of G_α subunits: $G_{q/11}\alpha$, $G_{12/13}\alpha$, $G_{i/o}\alpha$ (G inhibitory, G other), and $G_s\alpha$ (G stimulatory).

[00162] In some instances, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ and promote nuclear translocation. In other instances, $G_s\alpha$ (G stimulatory) coupled GPCRs suppress YAP/TAZ activity, leading to YAP/TAZ degradation.

[00163] In some cases, $G_i\alpha$ (G inhibitory), $G_o\alpha$ (G other), $G_{q/11}\alpha$, and $G_{12/13}\alpha$ coupled GPCRs activate YAP/TAZ through repression of Lats1/2 activities. In contrast, $G_s\alpha$, in some embodiments, induces Lats1/2 activity, thereby promoting YAP/TAZ degradation.

G_q Family

[00164] $G_q\alpha$ (also known as $G_{q/11}$ protein), participates in the inositol trisphosphate (IP_3) signal transduction pathway and calcium (Ca^{2+}) release from intracellular storage through the activation of phospholipase C (PLC). The activated PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and IP_3. In some instances, IP_3 then diffuses through the cytoplasm into the ER or the sarcoplasmic reticulum (SR) in the case of muscle cells, and then binds to inositol trisphosphate receptor (InsP3R), which is a Ca^{2+} channel. In some cases, the binding triggers the opening of the Ca^{2+} channel, and thereby increases the release of Ca^{2+} into the cytoplasm.

[00165] In some embodiments, the GPCRs that interact with $G_q\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT_2 and 5-HT_3; alpha-1 adrenergic receptor; vasopressin type 1 receptors 1A and 1B; angiotensin II receptor type 1; calcitonin receptor; histamine H1 receptor; metabotropic glutamate receptor, group I; muscarinic receptors M_1, M_3, and M_5; and trace amine-associated receptor 1.

[00166] In some instances, there are several types of $G_q\alpha$: G_q, $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$. The G_q protein is encoded by *GNAQ*. $G_{q/11}$ is encoded by *GNA11*. $G_{q/14}$ is encoded by *GNA14*. $G_{q/15}$ is encoded by *GNA15*.

[00167] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with cancer. Indeed, studies have shown that mutations in $G_q\alpha$ promote uveal melanoma (UM) tumorigenesis. In some instances, about 80% of UM cases have been detected to contain a mutation in *GNAQ* and/or *GNA11*.

[00168] In some instances, mutations or modifications of the $G_q\alpha$ genes have been associated with congenital diseases. In some instances, mutations of $G_q\alpha$ have been observed in congenital diseases such as Port-Wine Stain and/or Sturge-Weber Syndrome. In some instances, about 92% of Port-Wine stain cases harbors a mutation in *GNAQ*. In some instances, about 88% of Sturge-Weber Syndrome harbors a mutation in *GNAQ*.

$G_{12/13}$ Family

[00169] $G_{12/13}\alpha$ modulates actin cytoskeletal remodeling in cells and regulates cell processes through guanine nucleotide exchange factors (GEFs). GEFs participate in the activation of small GTPases which acts as molecular switches in a variety of intracellular signaling pathways. Examples of small GTPases include the Ras-related GTPase superfamily (e.g., Rho family such as Cdc42), which is involved in cell differentiation, proliferation, cytoskeletal organization, vesicle trafficking, and nuclear transport.

[00170] In some embodiments, the GPCRs that interact with $G_{12/13}\alpha$ include, but are not limited to, purinergic receptors (e.g. $P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$); muscarinic acetylcholine receptors M1 and M3; receptors for thrombin [protease-activated receptor (PAR)-1, PAR-2]; thromboxane (TXA2); sphingosine 1-phosphate (e.g. $S1P_2$, $S1P_3$, $S1P_4$ and $S1P_5$); lysophosphatidic acid (e.g. LPA_1, LPA_2, LPA_3); angiotensin II (AT1); serotonin ($5\text{-}HT_{2c}$ and $5\text{-}HT_4$); somatostatin (sst_5); endothelin (ET_A and ET_B); cholecystokinin (CCK_1); V_{1a} vasopressin receptors; D_5 dopamine receptors; fMLP formyl peptide receptors; GAL_2 galanin receptors; EP_3 prostanoid receptors; A_1 adenosine receptors; α_1 adrenergic receptors; BB_2 bombesin receptors; B_2 bradykinin receptors; calcium-sensing receptors; KSHV-ORF74 chemokine receptors; NK_1 tachykinin receptors; and thyroid-stimulating hormone (TSH) receptors.

[00171] In some instances, $G_{12/13}\alpha$ is further subdivided into G_{12} and G_{13} types which are encoded by *GNA12* and *GNA13*, respectively.

$G_{i/o}$ Family

[00172] $G_{i/o}\alpha$ (G inhibitory, G other) (also known as G_i/G_0 or G_i protein) suppresses the production of 3',5'-cyclic AMP (cAMP) from adenosine triphosphate (ATP) through an inhibition of adenylate cyclase activity, which converts ATP to cAMP.

[00173] In some embodiments, the GPCRs that interact with $G_i\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types $5\text{-}HT_1$ and $5\text{-}HT_5$; muscarinic acetylcholine

receptors such as M_2 and M_4; adenosine receptors such as A_1 and A_3; adrenergic receptors such as α_{2A}, α_{2B}, and α_{2C}; apelin receptors; calcium-sensing receptor; cannabinoid receptors CB1 and CB2; chemokine CXCR4 receptor; dopamines D_2, D_3, and D_4; $GABA_B$ receptor; glutamate receptors such as metabotropic glutamate receptor 2 (mGluR2), metabotropic glutamate receptor 3 (mGluR3), metabotropic glutamate receptor 4 (mGluR4), metabotropic glutamate receptor 6 (mGluR6), metabotropic glutamate receptor 7 (mGluR7), and metabotropic glutamate receptor 8 (mGluR8); histamine receptors such as H_3 and H_4 receptors; melatonin receptors such as melatonin receptor type 1 (MT1), melatonin receptor type 2 (MT2), and melatonin receptor type 3 (MT3); niacin receptors such as NIACR1 and NIACR2; opioid receptors such as δ, κ, μ, and nociceptin receptors; prostaglandin receptors such as prostaglandin E receptor 1 (EP_1), prostaglandin E receptor 3 (EP_3), prostaglandin F receptor (FP), and thromboxane receptor (TP); somatostatin receptors sst1, sst2, sst3, sst4, and sst5; and trace amine-associated receptor 8.

[00174] In some instances, there are several types of $G_i\alpha$: $G_i\alpha1$, $G_i\alpha2$, $G_i\alpha3$, $G_i\alpha4$, $G_o\alpha$, G_t, G_{gust}, and G_z. $G_i\alpha1$ is encoded by *GNAI1*. $G_i\alpha2$ is encoded by *GNAI2*. $G_i\alpha3$ is encoded by *GNAI3*. $G_o\alpha$, the a_o subunit, is encoded by *GNAO1*. G_t is encoded by *GNAT1* and *GNAT2*. G_{gust} is encoded by *GNAT3*. G_z is encoded by *GNAZ*.

G_s Family

[00175] $G_s\alpha$ (also known as G stimulatory, G_s alpha subunit, or G_s protein) activates the cAMP-dependent pathway through the activation of adenylate cyclase, which convers adenosine triphosphate (ATP) to 3',5'-cyclic AMP (cAMP) and pyrophosphate. In some embodiments, the GPCRs that interact with $G_s\alpha$ include, but are not limited to, 5-hydroxytryptamine receptor (5-HT receptor) types 5-HT_4, 5-HT_6, and 5-HT_7; adrenocorticotropic hormone receptor (ACTH receptor) (also known as melanocortin receptor 2 or MC2R); adenosine receptor types A_{2a} and A_{2b}; arginine vasopressin receptor 2 (AVPR2); β-adrenergic receptors β_1, β_2, and β_3; calcitonin receptor; calcitonin gene-related peptide receptor; corticotropin-releasing hormone receptor; dopamine receptor D_1-like family receptors such as D_1 and D_5; follicle-stimulating hormone receptor (FSH-receptor); gastric inhibitory polypeptide receptor; glucagon receptor; histamine H_2 receptor; luteinizing hormone/choriogonadotropin receptor; melanocortin receptors such as MC1R, MC2R, MC3R, MC4R, and MC5R; parathyroid hormone receptor 1; prostaglandin receptor types D_2 and I_2; secretin receptor; thyrotropin receptor; trace amine-associated receptor 1; and box jellyfish opsin.

[00176] In some instances, there are two types of $G_s\alpha$: G_s and G_{olf}. G_s is encoded by *GNAS*. G_{olf} is encoded by *GNAL*.

Additional Regulators of the Hippo signaling network

[00177] In some embodiments, the additional regulator of the Hippo signaling pathway is the Crumbs (Crb) complex. The Crumbs complex is a key regulator of cell polarity and cell shape. In some instances, the Crumbs complex comprises transmembrane CRB proteins which assemble multi-protein complexes that function in cell polarity. In some instances, CRB complexes recruit members of the Angiomotin (AMOT) family of adaptor proteins that interact with the Hippo pathway components. In some instances, studies have shown that AMOT directly binds to YAP, promotes YAP phosphorylation, and inhibits its nuclear localization.

[00178] In some instances, the additional regulator of the Hippo signaling pathway comprises regulators of the MST kinase family. MST kinases monitor actin cytoskeletal integrity. In some instances, the regulators include TAO kinases and cell polarity kinase PAR-1.

[00179] In some instances, the additional regulator of the Hippo signaling pathway comprises molecules of the adherens junction. In some instances, E-Cadherin (E-cad) suppresses YAP nuclear localization and activity through regulating MST activity. In some embodiments, E-cad-associated protein α-catenin regulates YAP through sequestering YAP/14-3-3 complexes in the cytoplasm. In other instances, Ajuba protein family members interact with Lats1/2 kinase activity, thereby preventing inactivation of YAP/TAZ.

[00180] In some embodiments, additional proteins that interact with YAP/TAZ either directly or indirectly include, but are not limited to, Merlin, protocadherin Fat 1, MASK1/2, HIPK2, PTPN14, RASSF, PP2A, Salt-inducible kinases (SIKs), Scribble (SCRIB), the Scribble associated proteins Discs large (Dlg), KIBRA, PTPN14, NPHP3, LKB1, Ajuba, and ZO1/2.

[00181] In some embodiments, the compounds described herein are inhibitors of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds described herein increase the phosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the dephosphorylation of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP). In some embodiments, the compounds increase the ubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP) or decrease the deubiquitination of transcriptional coactivator with PDZ binding motif/ Yes- associated protein transcriptional coactivator (TAZ/YAP).

[00182] In some embodiments, the compounds disclosed herein are inhibitors of one or more of the proteins encompassed by, or related to, the Hippo pathway. In some instances, the one or more proteins comprise a protein described above. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a G-protein and/or its coupled GPCR. In some embodiments, an inhibitor

of the Hippo pathway is an inhibitor of a G-protein. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of the $G_q\alpha$ family proteins such as G_q, $G_{q/11}$, $G_{q/14}$, and $G_{q/15}$; the $G_{12/13}\alpha$ family of proteins such as G_{12} and G_{13}; or the $G_i\alpha$ family of proteins such as $G_i\alpha1$, $G_i\alpha2$, $G_i\alpha3$, $G_i\alpha4$, $G_o\alpha$, G_t, G_{gust}, and G_z. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_q. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/11}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/14}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_{q/15}$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{12}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{13}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha1$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha2$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha3$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_i\alpha4$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of $G_o\alpha$. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_t. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_{gust}. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of G_z.

[00183] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a core protein of the Hippo pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Sav1. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Mob. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of YAP. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TAZ. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of TEtOAcD.

[00184] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein associated with the ubiquitination and proteasomal degradation pathway. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a proteasomal degradation pathway protein (e.g., 26S proteasome).

[00185] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein of the Ras superfamily of proteins. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a protein of the Rho family of proteins. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of Cdc42.

[00186] Cdc42 is a member of the Ras superfamily of small GTPases. Specifically, Cdc42 belongs to the Rho family of GTPases, in which the family members participate in diverse and critical cellular processes such as gene transcription, cell-cell adhesion, and cell cycle progression. Cdc42 is involved in cell growth and polarity, and in some instances, Cdc42 is activated by guanine

nucleotide exchange factors (GEFs). In some cases, an inhibitor of Cdc42 is a compound disclosed herein.

[00187] In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a deubiquitinating enzyme. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of a cysteine protease or a metalloprotease. In some embodiments, an inhibitor of the Hippo pathway is an inhibitor of an ubiquitin-specific protease. USP47 is a member of the ubiquitin-specific protease (USP/UBP) superfamily of cysteine proteases. In some embodiments, the compounds disclosed herein are inhibitors of USP47.

[00188] Further embodiments provided herein include combinations of one or more of the particular embodiments set forth above.

[00189] In another aspect, the present disclosure provides a method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00190] In another aspect, the present disclosure provides a method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject has cancer, polycystic kidney disease, or liver fibrosis. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[00191] In another aspect, the present disclosure provides a method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.

[00192] In another aspect, the present disclosure provides a method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00193] In yet another aspect, the present disclosure provides a method of treating or preventing a disease or disorder amenable to treatment with a compound that inhibits the activity of one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject in need thereof a therapeutically acceptable amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00194] In yet another aspect, the present disclosure provides a method of treating or preventing a disease or disorder amenable to treatment with a compound that inhibits transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject in need thereof a therapeutically acceptable amount of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof.

[00195] In yet another aspect, provided herein are uses of a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (III-a), (III-b), (III-c), (IV), (V), or (VI) as disclosed herein or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition thereof as described herein, in the preparation of a medicament for treating a disease or disorder (e.g., a disease or disorder conducive to treatment to prevention by inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof.

[00196] In another aspect, a compound disclosed herein is for use in a method of treating a disease or disorder (e.g., a disease or disorder amenable to treatment with a compound that inhibits one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof, such cancer. Such a compound is, for example, a compound of Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (III-a), (III-b), (III-c), (IV), (V), or (VI) as disclosed herein, or a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable excipient, as disclosed herein.

[00197] In another aspect, provided herein are pharmaceutical compositions comprising a compound Formula (I), (II-a), (II-b), (II-c), (II-d), (II-e), (II-f), (II-g), (II-h), (II-i), (II-j), (II-k), (III-

a), (III-b), (III-c), (IV), (V), or (VI) as disclosed herein or a pharmaceutically acceptable salt thereof, for use in treating a disease or disorder (e.g., a disease or disorder amenable to treatment with a compound that inhibits one or more of proteins encompassed by, or related to, the Hippo pathway; or a disease or disorder conducive to treatment to prevention by inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP)) in a subject in need thereof.

Diseases

Cancer

[00198] In some embodiments, the compounds disclosed herein are useful for treating cancer. In some embodiments, disclosed herein is a method for treating a cancer in a subject in need thereof comprising administering a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, disclosed herein is a compound for use in treating a cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of a compound disclosed herein or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the cancer is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes-associated protein transcription coactivator (TAZ/YAP). In some embodiments, the cancer is mediated by modulation of the interaction of YAP/TAZ with TEtOAcD. In some embodiments, the cancer is characterized by a mutant Gα-protein. In some embodiments, the mutant Gα-protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant Gα-protein is G12. In some embodiments, the mutant Gα-protein is G13. In some embodiments, the mutant Gα-protein is Gq. In some embodiments, the mutant Gα-protein is G11. In some embodiments, the mutant Gα-protein is Gi. In some embodiments, the mutant Gα-protein is Go. In some embodiments, the mutant Gα-protein is Gs.

[00199] In some embodiments, the cancer is a solid tumor. In some instances, the cancer is a hematologic malignancy. In some instances, the solid tumor is a sarcoma or carcinoma. In some instances, the solid tumor is a sarcoma. In some instances, the solid tumor is a carcinoma.

[00200] Exemplary sarcoma includes, but is not limited to, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastoma, angiosarcoma, chondrosarcoma, chordoma, clear cell sarcoma of soft tissue, dedifferentiated liposarcoma, desmoid, desmoplastic small round cell tumor, embryonal rhabdomyosarcoma, epithelioid fibrosarcoma, epithelioid hemangioendothelioma, epithelioid sarcoma, esthesioneuroblastoma, Ewing sarcoma, extrarenal rhabdoid tumor, extraskeletal myxoid chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, giant cell tumor, hemangiopericytoma, infantile fibrosarcoma, inflammatory myofibroblastic tumor, Kaposi

sarcoma, leiomyosarcoma of bone, liposarcoma, liposarcoma of bone, malignant fibrous histiocytoma (MFH), malignant fibrous histiocytoma (MFH) of bone, malignant mesenchymoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma, myxofibrosarcoma, myxoid liposarcoma, myxoinflammatory fibroblastic sarcoma, neoplasms with perivascular epithelioid cell differentiation, osteosarcoma, parosteal osteosarcoma, neoplasm with perivascular epithelioid cell differentiation, periosteal osteosarcoma, pleomorphic liposarcoma, pleomorphic rhabdomyosarcoma, PNET/extraskeletal Ewing tumor, rhabdomyosarcoma, round cell liposarcoma, small cell osteosarcoma, solitary fibrous tumor, synovial sarcoma, and telangiectatic osteosarcoma.

[00201] Exemplary carcinoma includes, but is not limited to, adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer. In some instances, the liver cancer is primary liver cancer.

[00202] In some instances, the cancer is selected from uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the cancer is uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the cancer is uveal melanoma. In some cases, the cancer is mesothelioma. In some cases, the cancer is esophageal cancer. In some cases, the cancer is liver cancer. In some cases, the cancer is primary liver cancer.

[00203] In some instances, the cancer is a hematologic malignancy. In some embodiments, a hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some instances, a hematologic malignancy is a T-cell malignancy. Exemplary T-cell malignancy includes, but is not

limited to, peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, and treatment-related T-cell lymphomas.

[00204] In some instances, a hematologic malignancy is a B-cell malignancy. Exemplary B-cell malignancy includes, but is not limited to, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, and a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00205] In some instances, the cancer is a relapsed or refractory cancer. In some embodiments, the relapsed or refractory cancer is a relapsed or refractory solid tumor. In some embodiments, the relapsed or refractory solid tumor is a relapsed or refractory sarcoma or a relapsed or refractory carcinoma. In some embodiments, the relapsed or refractory carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00206] In some instances, the relapsed or refractory cancer is selected from relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, liver

cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory uveal melanoma. In some cases, the relapsed or refractory cancer is relapsed or refractory mesothelioma. In some cases, the relapsed or refractory cancer is relapsed or refractory esophageal cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory liver cancer. In some cases, the relapsed or refractory cancer is relapsed or refractory primary liver cancer.

[00207] In some instances, the relapsed or refractory cancer is a relapsed or refractory hematologic malignancy. In some embodiments, a relapsed or refractory hematologic malignancy is a relapsed or refractory leukemia, a relapsed or refractory lymphoma, a relapsed or refractory myeloma, a relapsed or refractory non-Hodgkin's lymphoma, a relapsed or refractory Hodgkin's lymphoma, a relapsed or refractory T-cell malignancy, or a relapsed or refractory B-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory T-cell malignancy. In some instances, a relapsed or refractory hematologic malignancy is a relapsed or refractory B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

[00208] In some instances, the cancer is a metastasized cancer. In some instances, the metastasized cancer is a metastasized solid tumor. In some instances, the metastasized solid tumor is a metastasized sarcoma or a metastasized carcinoma. In some embodiments, the metastasized carcinoma includes adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, anaplastic carcinoma, large cell carcinoma, small cell carcinoma, anal cancer, appendix cancer, bile duct cancer (i.e., cholangiocarcinoma), bladder cancer, brain tumor, breast cancer, cervical cancer, colon cancer, cancer of Unknown Primary (CUP), esophageal cancer, eye cancer, fallopian tube

cancer, gastroenterological cancer, kidney cancer, liver cancer, lung cancer, medulloblastoma, melanoma, oral cancer, ovarian cancer, pancreatic cancer, parathyroid disease, penile cancer, pituitary tumor, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, throat cancer, thyroid cancer, uterine cancer, vaginal cancer, and vulvar cancer.

[00209] In some instances, the metastasized cancer is selected from metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, and meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, colorectal cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer, or meningioma. In some cases, the metastasized cancer is metastasized uveal melanoma, mesothelioma, esophageal cancer, or liver cancer. In some cases, the metastasized cancer is metastasized uveal melanoma. In some cases, the metastasized cancer is metastasized mesothelioma. In some cases, the metastasized cancer is metastasized esophageal cancer. In some cases, the metastasized cancer is metastasized liver cancer. In some cases, the metastasized cancer is metastasized primary liver cancer.

[00210] In some instances, the metastasized cancer is a metastasized hematologic malignancy. In some embodiments, the metastasized hematologic malignancy is a metastasized leukemia, a metastasized lymphoma, a metastasized myeloma, a metastasized non-Hodgkin's lymphoma, a metastasized Hodgkin's lymphoma, a metastasized T-cell malignancy, or a metastasized B-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized T-cell malignancy. In some instances, a metastasized hematologic malignancy is a metastasized B-cell malignancy, such as for example, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, or a non-CLL/SLL lymphoma. In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, or lymphomatoid granulomatosis.

Congenital Diseases

[00211] In some embodiments, the compounds disclosed herein are useful for treating a congenital disease. In some embodiments, the congenital disease is mediated by activation of transcriptional coactivator with PDZ binding motif/Yes- associated protein transcription coactivator (TAZ/YAP). In some embodiments, the congenital disease is characterized by a mutant Gα-protein. In some embodiments, the mutant Gα-protein is selected from G12, G13, Gq, G11, Gi, Go, and Gs. In some embodiments, the mutant Gα-protein is G12. In some embodiments, the mutant Gα-protein is G13. In some embodiments, the mutant Gα-protein is Gq. In some embodiments, the mutant Gα-protein is G11. In some embodiments, the mutant Gα-protein is Gi. In some embodiments, the mutant Gα-protein is Go. In some embodiments, the mutant Gα-protein is Gs.

[00212] In some embodiments, the congenital disease is the result of a genetic abnormality, an intrauterine environment, errors related to morphogenesis, infection, epigenetic modifications on a parental germline, or a chromosomal abnormality. Exemplary congenital diseases include, but are not limited to, Sturge-Weber Syndrome, Port-Wine stain, Holt-Oram syndrome, abdominal wall defects, Becker muscular dystrophy (BMD), biotinidase deficiency, Charcot-Marie-Tooth (CMT), cleft lip, cleft palate, congenital adrenal hyperplasia, congenital heart defects, congenital hypothyroidism, congenital muscular dystrophy, cystic fibrosis, Down syndrome, Duchenne muscular dystrophy, Fragile X syndrome, Friedreich's ataxia, galactosemia, hemoglobinopathies, Krabbe disease, limb-girdle muscular dystrophy, medium chain acyl-CoA dehydrogenase deficiency, myasthenia gravis, neural tube defects, phenylketonuria, Pompe disease, severe combined immunodeficiency (SCID), Stickler syndrome (or hereditary progressive arthro-ophthalmopathy), spinal muscular atrophy, and trisomy 18. In some embodiments, the congenital disease is Sturge-Weber Syndrome or Port-Wine stain. In some embodiments, the congenital disease is Sturge-Weber Syndrome. In some embodiments, the congenital disease is Port-Wine stain.

EXAMPLES

[00213] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

List of abbreviations

[00214] As used above, and throughout the disclosure, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN	acetonitrile
Ac	acetyl

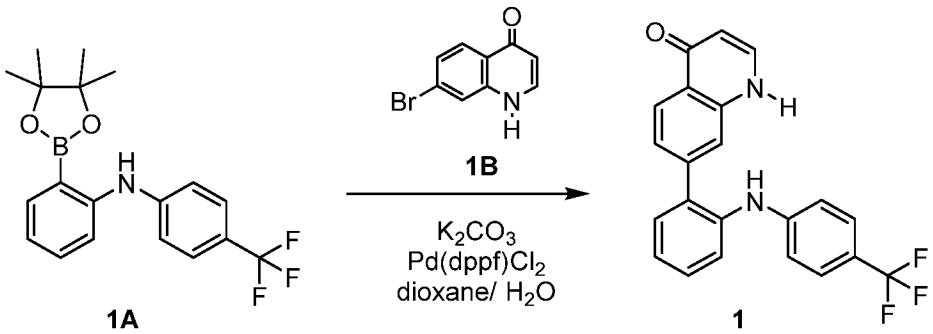
BOC or Boc	*tert*-butyl carbamate
t-Bu	*tert*-butyl
°C	degrees Celsius
DBA or dba	dibenzylideneacetone
DCE	dichloroethane ($ClCH_2CH_2Cl$)
DCM	dichloromethane (CH_2Cl_2)
DIPEtOAc or DIEtOAc	diisopropylethylamine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc or EtOAc	ethyl acetate
Et	ethyl
EtOH	ethanol
g	gram(s)
h, hr, hrs	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
LC-MS	liquid chromatography mass spectrometry
m/z	mass-to-charge ratio
M	molar
Me	methyl
MeOH	methanol
mg	milligram(s)
MHz	megahertz
µmol	micromole(s)
uL	microliter(s)
mL	milliliter(s)
mmol	millimole(s)
MS	mass spectroscopy
NMR	nuclear magnetic resonance
PE	petroleum ether
Ph	phenyl
prep-HPLC	preparative high pressure liquid chromatography
prep-TLC	preparative thin layer chromatography
Py	pyridine

RT	retention time
TEtOAc	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

I. Chemical Synthesis

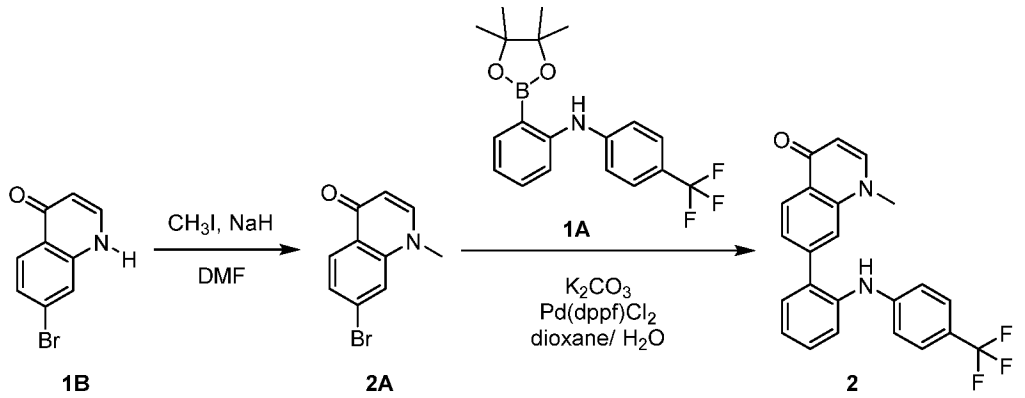
[00215] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Anhydrous solvents and oven-dried glassware were used for synthetic transformations sensitive to moisture and/or oxygen. Yields were not optimized. Reaction times were approximate and were not optimized. Column chromatography and thin layer chromatography (TLC) were performed on silica gel unless otherwise noted.

Example 1: 7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one (Compound 1)



[00216] To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (**1A**, 50.0 mg, 0.14 mmol, 1 *eq*), 7-bromoquinolin-4(1*H*)-one (**1B**, 33.9 mg, 0.15 mmol, 1.1 *eq*) and K_2CO_3 (38.1 mg, 0.28 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was added Pd(dppf)Cl_2 (5.0 mg, 6.9 umol, 0.05 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the mixture was stirred at 80 °C for 16 hr under N_2. The reaction mixture was quenched by H_2O (10 mL) and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 50 10u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 45%-75%, 7.8min) to afford **Compound 1** (10.3 mg, 19.8% yield) as a white solid. LC-MS (ESI): RT = 0.883 min, mass calc. for $C_{22}H_{15}F_3N_2O$ 380.11, m/z found 381.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-*d6)* δ 11.75 (br s, 1H), 8.12 - 8.01 (m, 2H), 7.88 (br s, 1H), 7.56 (s, 1H), 7.46 - 7.39 (m, 5H), 7.34 - 7.23 (m, 2H), 6.92 (br d, *J* = 8.4 Hz, 2H), 6.02 (br d, *J* = 7.1 Hz, 1H).

Example 2: 1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one (Compound 2)



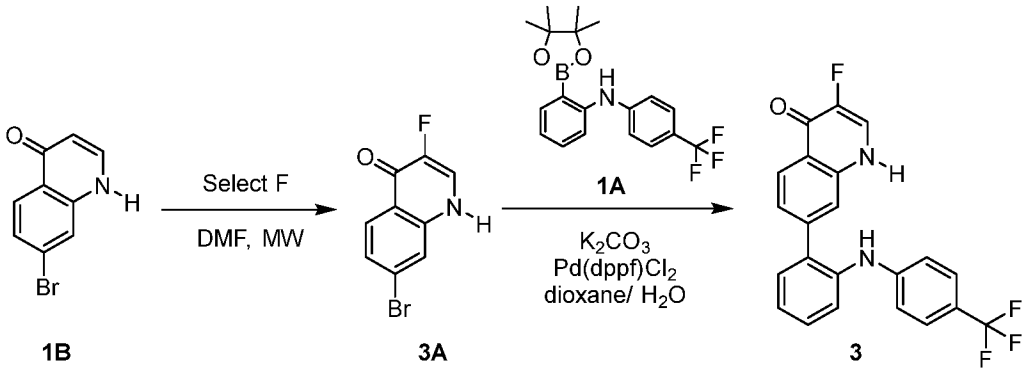
7-bromo-1-methylquinolin-4(1*H*)-one

[00217] To a solution of 7-bromoquinolin-4(1*H*)-one (**1B**, 100.0 mg, 0.45 mmol, 1 *eq*) in DMF (2 mL) was added NaH (35.7 mg, 0.89 mmol, 60%, 2 *eq*). The reaction mixture was stirred at 20°C for 0.5 hr. MeI (126.7 mg, 0.89 mmol, 56 uL, 2 *eq*) was added. The reaction mixture was further stirred at 20 °C for 0.5 hr. The reaction mixture was quenched with H_2O (5 mL). The mixture was extracted with EtOAc (10 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated to give intermediate **2A** (60.0 mg, crude) as a yellow solid, which was used in the next step without further purification.

methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1*H*)-one

[00218] To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)phenyl)aniline (**1A**, 50.0 mg, 0.14 mmol, 1 *eq*), intermediate **2A** (36.1 mg, 0.15 mmol, 1.1 *eq*) and K_2CO_3 (38.1 mg, 0.28 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) was added Pd(dppf)Cl_2 (5.0 mg, 6.9 umol, 0.05 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 16 hr under N_2. The reaction mixture was quenched by H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC (column: Waters Xbridge 150 x 50 10u; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 47%-77%, 7.8min) to afford **Compound 2** (5.7 mg, 10.5% yield) as a white solid. LC-MS (ESI): RT = 0.798 min, mass calc. for $C_{23}H_{17}F_3N_2O$ 394.13, m/z found 394.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.13 (d, J = 4.3 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.59 - 7.54 (m, 2H), 7.49 - 7.37 (m, 5H), 7.35 - 7.30 (m, 1H), 6.84 (d, J = 8.5 Hz, 2H), 6.01 (d, J = 7.8 Hz, 1H), 3.66 (s, 3H).

Example 3: 3-Fluoro-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one (Compound 3)



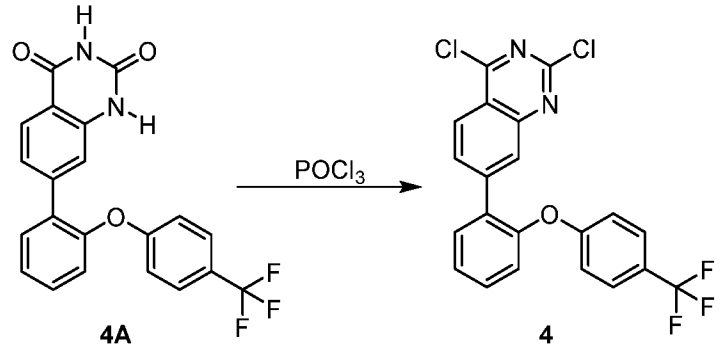
7-Bromo-3-fluoroquinolin-4(1*H*)-one

[00219] 7-Bromoquinolin-4(1*H*)-one (**1B**, 200 mg, 0.89 mmol, 1 *eq*) and Select F (347.8 mg, 0.98 mmol, 1.1 *eq*) were taken up into a microwave tube in DMF (4 mL) .The sealed tube was heated at 120 °C for 1 hr under microwave. The reaction mixture was concentrated under reduced pressure. The reaction mixture was diluted with water (20 mL) and the resultant mixture was extracted with EtOAc (40 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by column chromatography over silica gel (DCM: MeOH = 1:0 to 10:1) to give intermediate **3A** (70 mg, 0.21 mmol, 24.3% yield) as a yellow solid.

3-Fluoro-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1*H*)-one

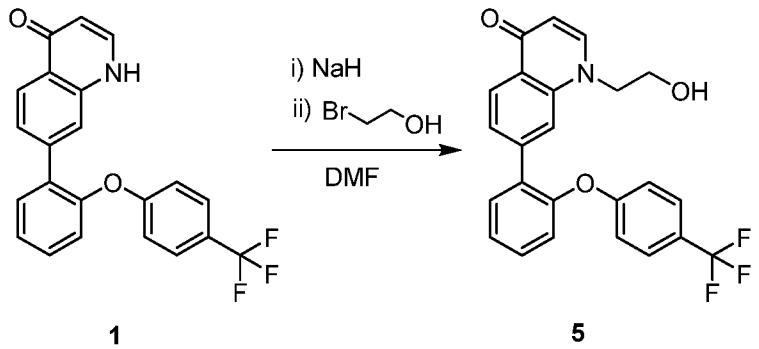
[00220] To a solution of 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-[4-(trifluoromethyl)phenyl]aniline (**1A**, 100 mg, 0.27 mmol, 1 *eq*), 7 intermediate **3A** (70 mg, 0.29 mmol, 1.05 *eq*) and Na_2CO_3 (58.3 mg, 0.55 mmol, 2 *eq*) in dioxane (2.5 mL) and H_2O (0.5 mL) was added $Pd(dppf)Cl_2$ (10.0 mg, 13 umol, 0.05 *eq*) under N_2. The reaction mixture was stirred at 90 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with water (20 mL) and the resultant mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 x 25mm x 5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 40%-70%, 9.5min) to afford **Compound 3** (19.0 mg, 17.2% yield) as a white solid. LC-MS (ESI): RT =0.892 min, mass calcd for $C_{22}H_{14}F_4N_2O$ 398.10 m/z, found 399.0 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 11.95 (br s, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H), 7.63 (d, J = 1.0 Hz, 1H), 7.47 - 7.39 (m, 5H), 7.35 (dd, J = 1.2, 8.4 Hz, 1H), 7.31 - 7.24 (m, 1H), 6.93 (d, J = 8.6 Hz, 2H).

Example 4: 2,4-Dichloro-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinazoline (Compound 4)



[00221] A mixture of compound **4A** (360 mg, 0.90 mmol, 1 *eq*) and $POCl_3$ (15.4 g, 100.57 mmol, 9.35 mL, 111.27 *eq*) was stirred at 115 °C for 12 hrs. The reaction mixture was concentrated and adjusted to pH = 7~8 with saturated $NaHCO_3$ at 0 °C. The reaction mixture was diluted with water (15 mL), extracted with EtOAc (40 mL x 3). T he combined organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered and concentrated to give a residue, which was purified by column chromatography on silica gel (SiO_2, Ethyl acetate/Petroleum ether = 0% to 8%) to afford **Compound 4** (340 mg, 85.5% yield) as a white solid. LC-MS (ESI): RT = 1.132 min, mass calcd. for : $C_{21}H_{11}Cl_2F_3N_2O$ 434.02, m/z found 434.9 $[M+H]^+$; ^1H NMR (400 MHz, CD_3Cl) δ 8.22 (d, *J* = 8.8 Hz, 1H), 8.15 (d, *J* = 1.3 Hz, 1H), 7.92 (dd, *J* = 1.6, 8.7 Hz, 1H), 7.58 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.54 - 7.45 (m, 3H), 7.42 - 7.34 (m, 1H), 7.13 (dd, *J* = 0.9, 8.2 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H).

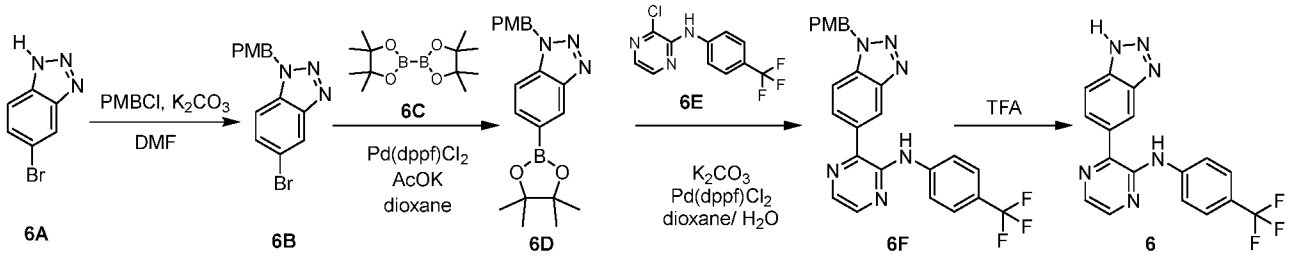
Example 5: 1-(2-Hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one (Compound 5)



[00222] To a solution of **Compound 1** (50 mg, 0.13 mmol, 1 *eq*) in DMF (1 mL) was added NaH (10.5 mg, 0.26 mmol, 60% purity, 2 *eq*) at 0 °C. The reaction mixture was stirred at 20 °C for 0.5 h. 2-Bromoethan-1-ol (19.7 mg, 0.16 mmol, 11 uL, 1.2 *eq*) was added into the reaction mixture. The mixture was stirred at 80 °C for 2 hrs. The mixture was concentrated and diluted

with H_2O (10 mL), and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 x 25mm x 5um; mobile phase: [water (0.05% ammonia hydroxide v/v)-ACN]; B%: 40%-70%, 9.5 min) to afford **Compound 5** (4.9 mg, 8.8% yield) as a white solid. LC-MS (ESI): RT = 0.863 min, mass calc. for $C_{24}H_{18}F_3NO_3$ 425.12, m/z found 426.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.77 (s, 1H), 7.71 - 7.61 (m, 3H), 7.60 - 7.40 (m, 3H), 7.23 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.5 Hz, 2H), 6.02 (d, J = 7.8 Hz, 1H), 4.98 (t, J = 5.4 Hz, 1H), 4.22 (br t, J = 5.0 Hz, 2H), 3.60 (br d, J = 5.1 Hz, 2H).

Example 6: 3-(1*H*-benzo[d][1,2,3]triazol-5-yl)-*N*-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 6)



5-bromo-1-[(4-methoxyphenyl)methyl]benzotriazole

[00223] To a mixture of 5-bromo-1H-benzo[d][1,2,3]triazole (**6A**, 1 g, 5.05 mmol, 1 *eq*) and PMBCl (1.19 g, 7.57 mmol, 1.03 mL, 1.5 *eq*) in DMF (10 mL) was added K_2CO_3 (1.40 g, 10.10 mmol, 2 *eq*). The mixture was stirred at 25 °C for 2 hrs. The mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give intermedieate **6B** (1.45 g, 3.51 mmol, 69.5% yield) as yellow oil. LC-MS (ESI): RT = 0.850 min, mass calc. for $C_{14}H_{12}BrN_3O$ 317.02, m/z found 317.9 $[M+H]^+$.

1-[(4-methoxyphenyl)methyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotriazole

[00224] To a solution of intermedieate **6B** (950 mg, 2.99 mmol, 1 *eq*) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (**6C**, 1.14 g, 4.48 mmol, 1.5 *eq*) in dioxane (10 mL) were added AcOK (586.1 mg, 5.97 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (109.2 mg, 0.15 mmol, 0.05 *eq*). The

reaction mixture was degassed and purged with N_2 for 3 times, then the mixture was stirred at 90 °C for 6 hr under N_2. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give intermediate **6D** (650 mg, 1.09 mmol, 36.4% yield) as a white solid. LC-MS (ESI): RT = 0.979 min, mass calc. for $C_{20}H_{24}BN_3O_3$ 365.19, m/z found 366.3 $[M+H]^+$.

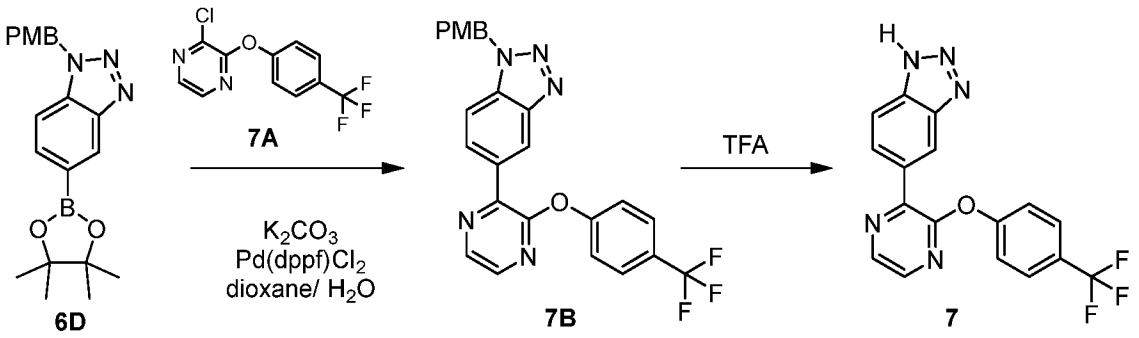
3-[1-[(4-methoxyphenyl)methyl]benzotriazol-5-yl]-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

[00225] To a solution of 3-chloro-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (**6E**, 100 mg, 0.37 mmol, 1 *eq*) and intermediate **6D** (200.2 mg, 0.55 mmol, 1.5 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (26.7 mg, 36.5 umol, 0.1 *eq*) and K_2CO_3 (101.0 mg, 0.73 mmol, 2 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 90 °C for 6 hrs under N_2. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica gel (ISCO®;12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **6F** (120 mg, 0.23 mmol, 63.4% yield) as a yellow oil. LC-MS (ESI): RT =1.010 min, mass calc. for $C_{25}H_{19}F_3N_6O$ 476.16, m/z found 477.3 $[M+H]^+$.

3-(1H-benzotriazol-5-yl)-N-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

[00226] A mixture of intermediate **6F** (120 mg, 0.25 mmol, 1 *eq*) in TFA (1.5 mL) was stirred at 70 °C for 8 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 40%-70%, 6.5 min) to afford **Compound 6** (17.6 mg, 19.5% yield) as a yellow solid. LC-MS (ESI): RT = 0.884 min, mass calc. for $C_{17}H_{11}F_3N_6$ 356.10, m/z found 357.2 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) 8.92 (s, 1H), 8.30 - 8.21 (m, 3H), 8.03 (d, J = 8.5 Hz, 1H), 7.81 - 7.70 (m, 3H), 7.59 (d, J = 8.8 Hz, 2H).

Example 7: 5-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)-1*H*-benzo[d][1,2,3]triazole (Compound 7)



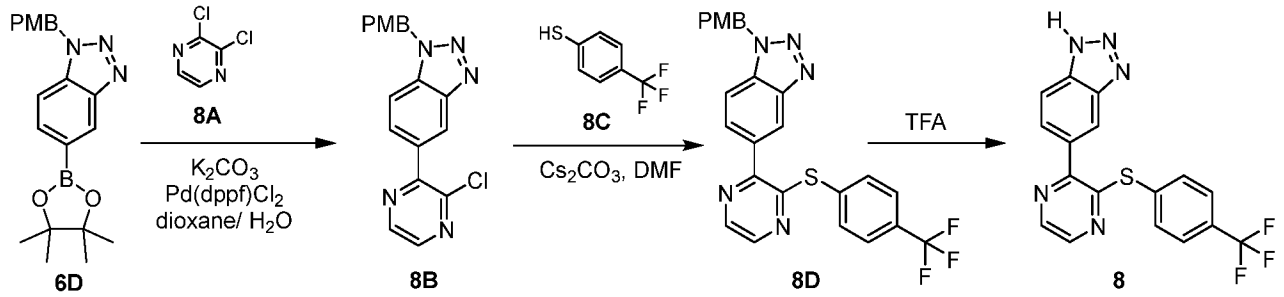
1-[(4-methoxyphenyl)methyl]-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]benzotriazole

[00227] To a solution of intermediate **6D** (80 mg, 0.29 mmol, 1 *eq*) and 2-chloro-3-(4-(trifluoromethyl)phenoxy)pyrazine (**7A**, 212.8 mg, 0.29 mmol, 1 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (21.3 mg, 29.1 umol, 0.1 *eq*) and K_2CO_3 (80.5 mg, 0.58 mmol, 2 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 90 °C for 6 hrs under N_2. The mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **7B** (40 mg, 78.8 umol, 27.0% yield) as a yellow oil. LC-MS (ESI): RT =1.003 min, mass calc. for $C_{25}H_{18}F_3N_5O_2$ 477.14, m/z found 478.3 $[M+H]^+$.

5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-1H-benzotriazole

[00228] A mixture of intermediate **7B** (20 mg, 41.9 umol, 1 *eq*) in TFA (0.5 mL) was stirred at 70 °C for 8 hrs. The mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water (0.05%HCl)-ACN]; B%: 35%-65%, 8.5 min) to afford **Compound 7** (10.7 mg, 30.0 umol, 71.7% yield, 100% purity) as a white solid. LC-MS (ESI): RT = 0.885 min, mass calc. for $C_{17}H_{10}F_3N_5O$ 357.08, m/z found 358.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) 8.81 (br s, 1H), 8.49 (br s, 1H), 8.31 (br s, 1H), 8.11 (s, 1H), 8.07 - 7.92 (m, 1H), 7.72 (br d, J = 7.3 Hz, 2H), 7.32 (br d, J = 7.5 Hz, 2H).

Example 8: 5-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1*H*-benzo[d][1,2,3]triazole (Compound 8)



5-(3-chloropyrazin-2-yl)-1-[(4-methoxyphenyl)methyl]benzotriazole

[00229] To a solution of intermediate **6D** (200 mg, 0.55 mmol, 1 *eq*) and 2,3-dichloropyrazine (**8A**, 122.4 mg, 0.82 mmol, 1.5 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (40.1 mg, 54.8 umol, 0.1 *eq*) and K_2CO_3 (151.4 mg, 1.10 mmol, 2 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 90 °C for 6 hours under N_2. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~42.5% Ethyl acetate/Petroleum ether gradient @ 20 mL/min) to give intermediate **8B** (100 mg, 0.26 mmol, 47.2% yield) as a colorless oil. LC-MS (ESI): RT = 0.869 min, mass calc. for $C_{18}H_{14}ClN_5O$ 351.09, m/z found 352.2 $[M+H]^+$.

1-[(4-methoxyphenyl)methyl]-5-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]benzotriazole

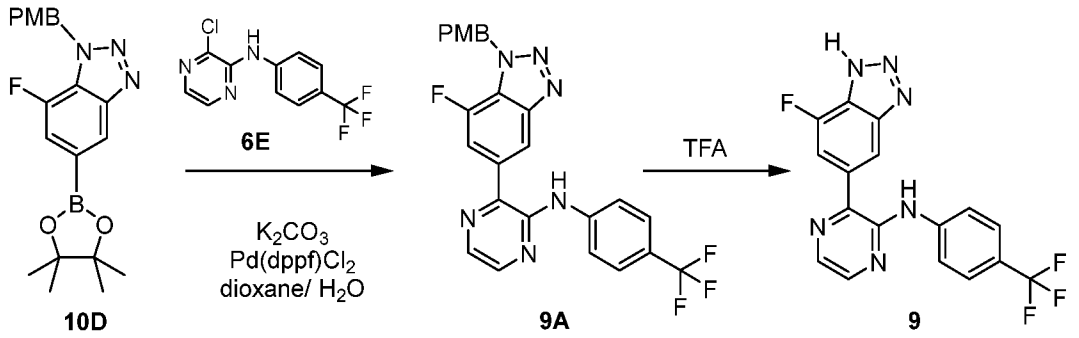
[00230] To a mixture of intermediate **8B** (100 mg, 0.28 mmol, 1 *eq*) and 4-(trifluoromethyl)benzenethiol (**8C**, 76.0 mg, 0.43 mmol, 1.5 *eq*) in DMF (1 mL) was added Cs_2CO_3 (185.2 mg, 0.57 mmol, 2 *eq*). The reaction mixture was stirred at 100 °C for 2 hours under N_2. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with H_2O (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **8D** (133.5 mg, crude) as a white solid. LC-MS (ESI): RT = 1.008 min, mass calc. for $C_{25}H_{18}N_5OSF_3$ 493.12, m/z found 494.3 $[M+H]^+$.

5-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]-1H-benzotriazole

[00231] A mixture of intermediate **8D** (130 mg, 0.26 mmol, 1 *eq*) in TFA (1 mL) was stirred at 70 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um;

mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 6.5 min) to afford **Compound 8** (15.7 mg, 15.9% yield) as a white solid. LC-MS (ESI): RT = 0.880 min, mass calc. for $C_{17}H_{10}N_5SF_3$ 373.06, m/z found 374.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) 8.56 (s, 1H), 8.44 (d, J = 2.0 Hz, 1H), 8.31 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.84 - 7.63 (m, 5H).

Example 9: 3-(7-Fluoro-1*H*-benzo[d][1,2,3]triazol-5-yl)-*N*-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 9)



3-[7-fluoro-1-[(4-methoxyphenyl)methyl]benzotriazol-5-yl]-*N*-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

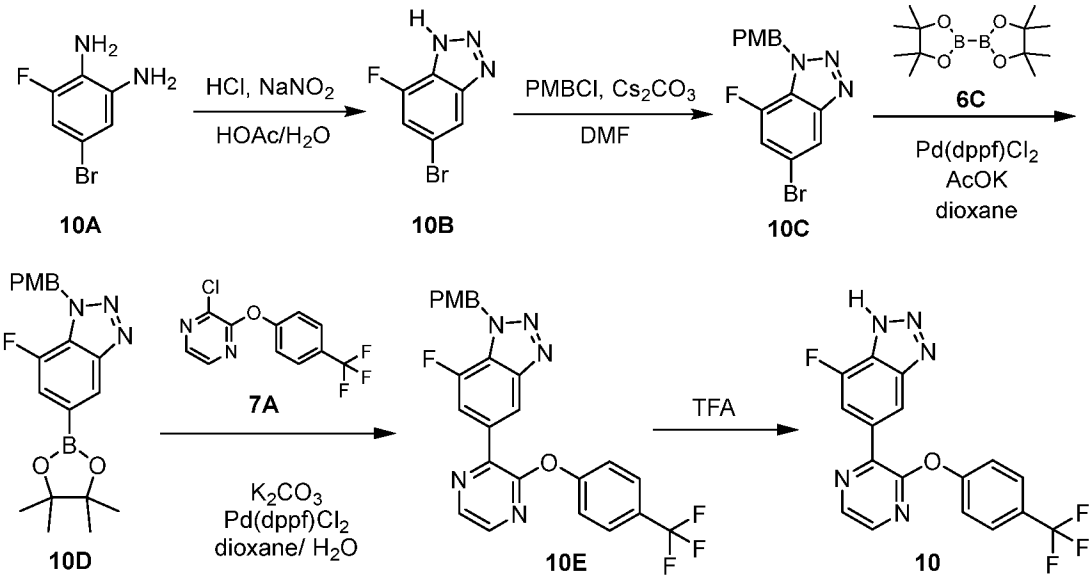
[00232] To a solution of 7-fluoro-1-(4-methoxybenzyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**10D**, 400 mg, 0.43 mmol, 1 *eq*) and 3-chloro-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (**6E**, 117.1 mg, 0.43 mmol, 1 *eq*) in dioxane (4 mL) and H_2O (1 mL) were added $Pd(dppf)Cl_2$ (31.3 mg, 42.8 umol, 0.1 *eq*) and K_2CO_3 (118.3 mg, 0.86 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the mixture was stirred at 90 °C for 6 hrs under N_2. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **9A** (180 mg, 0.35 mmol, 80.8% yield) as a yellow solid. LC-MS (ESI): RT = 0.976 min, mass calc. for $C_{25}H_{18}F_4N_6O$ 494.15, m/z found 495.1 $[M+H]^+$.

3-(7-fluoro-*1H*-benzotriazol-5-yl)-*N*-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

[00233] A mixture of intermediate **9A** (150 mg, 0.30 mmol, 1 *eq*) in TFA (2 mL) was stirred at 70 °C for 6 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 6.5 min) to afford **Compound 9** (40.7 mg, 35.9% yield) as a yellow solid. LC-MS (ESI): RT = 0.841 min, mass calc. for $C_{17}H_{10}F_4N_6$ 374.09,

m/z found 375.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 8.94 (s, 1H), 8.27 (s, 2H), 8.07 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.64 - 7.53 (m, 3H).

Example 10: 7-Fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole (Compound 10)



5-bromo-7-fluoro-1H-benzotriazole

[00234] To a solution of 5-bromo-3-fluorobenzene-1,2-diamine (**10A**, 1 g, 4.88 mmol, 1 *eq*) in acetic acid (7.5 mL) and H_2O (2.5 mL) were added $NaNO_2$ (504.8 mg, 7.32 mmol, 1.5 *eq*) and HCl (12 M, 0.41 mL, 1 *eq*) at 0 °C. The mixture was stirred at 0 °C for 2 hrs. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **10B** (1.35 g, crude) as a gray solid. LC-MS (ESI): RT = 0.757 min, mass calc. for C_6H_3BrFN 214.95, m/z found 216.1 $[M+H]^+$.

5-bromo-7-fluoro-1-[(4-methoxyphenyl)methyl]benzotriazole

[00235] To a mixture of intermediate **10B** (0.95 g, 4.40 mmol, 1 *eq*) and PMBCl (1.03 g, 6.60 mmol, 0.90 mL, 1.5 *eq*) in DMF (10 mL) was added Cs_2CO_3 (4.30 g, 13.19 mmol, 3 *eq*). The reaction mixture was stirred at 25 °C for 4 hrs. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~6.5% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **10C**

(800 mg, 1.88 mmol, 42.7% yield) as a white solid. LC-MS (ESI): RT = 0.952 min, mass calc. for $C_{14}H_{11}N_3FBrO$ 335.01, m/z found 336.1 $[M+H]^+$.

7-fluoro-1-[(4-methoxyphenyl)methyl]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzotriazole

[00236] To a mixture of intermediate **10C** (400 mg, 1.19 mmol, 1 *eq*) and **6C** (453.3 mg, 1.78 mmol, 1.5 *eq*) in dioxane (5 mL) were added AcOK (233.6 mg, 2.38 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (43.5 mg, 59.5 umol, 0.05 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times, then the mixture was stirred at 90 °C for 6 hrs under N_2. The mixture was diluted with H_2O (30 mL), extracted with EtOAc (60mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient @ 30 mL/min) to give intermediate **10D** (600 mg, 0.53 mmol, 44.7% yield, 34% purity) as a white solid. LC-MS (ESI): RT = 1.010 min, mass calc. for $C_{20}H_{23}N_3FBO_3$ 383.18, m/z found 384.3 $[M+H]^+$.

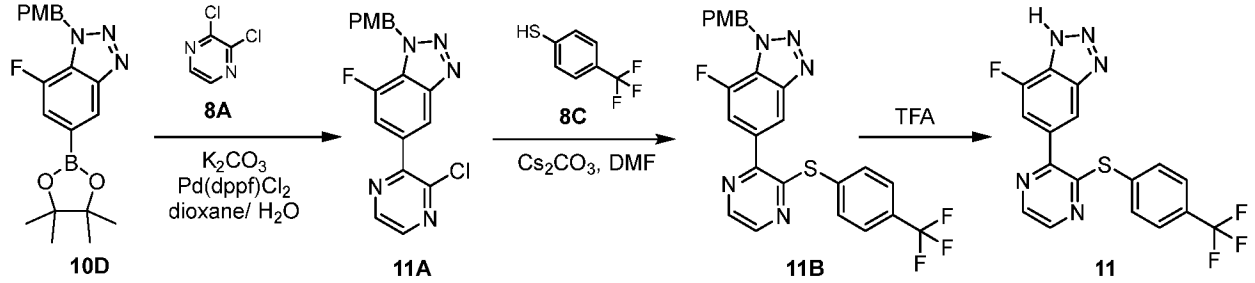
7-fluoro-1-[(4-methoxyphenyl)methyl]-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]benzotriazole

[00237] To a solution of intermediate **10D** (600 mg, 0.53 mmol, 1 *eq*) and **7A** (219.3 mg, 0.80 mmol, 1.5 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (19.5 mg, 26.6 umol, 0.05 *eq*) and K_2CO_3 (147.1 mg, 1.06 mmol, 2 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 3 times. The mixture was stirred at 90 °C for 6 hrs under N_2. The mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **10E** (300 mg, crude) as a red solid. LC-MS (ESI): RT = 1.031 min, mass calc. for $C_{25}H_{18}N_6OF_4$ 495.13, m/z found 496.3 $[M+H]^+$.

7-fluoro-5-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-1H-benzotriazole

[00238] A mixture of intermediate **10E** (298.03 mg, 0.5 mmol, 1 *eq*) in TFA (5 mL) was stirred at 70°C for 3 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water(0.05% HCl)-ACN];B%: 40%-70%,8.5 min) to afford **Compound 10** (107.4 mg, 62.2% yield) as a yellow solid. LC-MS (ESI): RT=0.913 min, macs calc. For $C_{17}H_9N_5OF_4$ 375.07, m/z found 376.2 $[M+H]^+$.

Example 11: 7-Fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1*H*-benzo[d][1,2,3]triazole (Compound 11)



5-(3-chloropyrazin-2-yl)-7-fluoro-1-[(4-methoxyphenyl)methyl]benzotriazole

[00239] To a solution of intermediate 10D (220 mg, 0.57 mmol, 1 *eq*) and 2,3-dichloropyrazine (8A, 128.3 mg, 0.86 mmol, 1.5 *eq*) in dioxane (2 mL) and H_2O (0.5 mL) were added $Pd(dppf)Cl_2$ (42.0 mg, 57.4 umol, 0.1 *eq*) and K_2CO_3 (158.7 mg, 1.15 mmol, 2 *eq*). The reaction mixture was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 90 °C for 6 hrs under N_2. The reaction mixture was diluted with H_2O (20 mL), extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~45% Ethyl acetate/Petroleum ether gradient @ 25 mL/min) to give intermediate **11A** (95 mg, 0.21 mmol, 35.8% yield) as a brown oil. LC-MS (ESI): RT = 0.833 min, mass calc. for $C_{18}H_{13}ClFN_5O$ 369.08, m/z found 370.0 $[M+H]^+$.

7-fluoro-1-[(4-methoxyphenyl)methyl]-5-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]benzotriazole

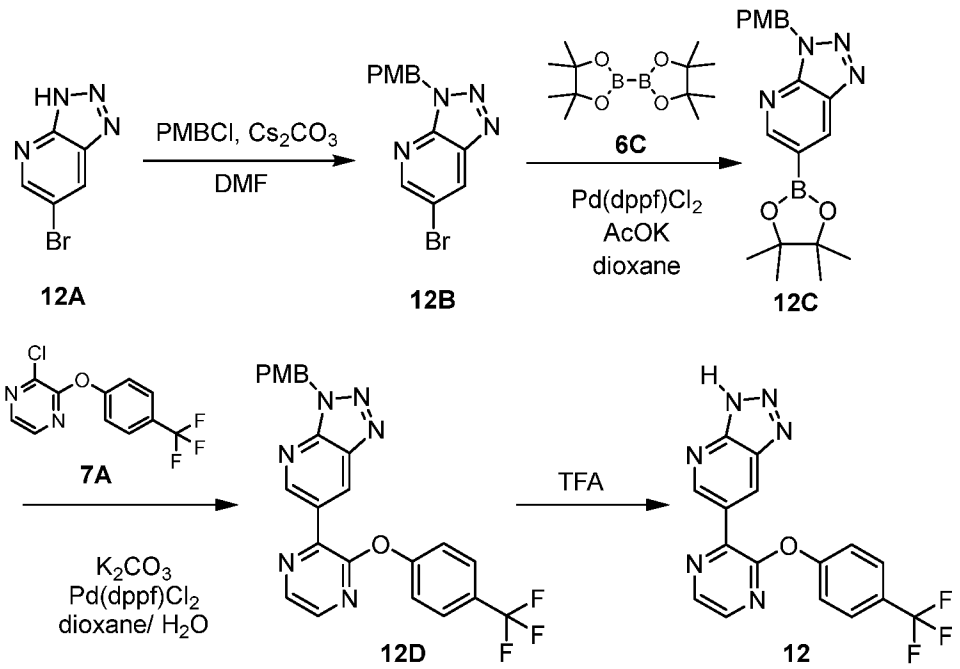
[00240] To a mixture of intermediate **11A** (95 mg, 0.26 mmol, 1 *eq*) and 4-(trifluoromethyl)benzenethiol (**8C**, 68.7 mg, 0.39 mmol, 1.5 *eq*) in DMF (1 mL) was added Cs_2CO_3 (167.4 mg, 0.51 mmol, 2 *eq*). The reaction mixture was stirred at 100 °C for 2 hrs. The reaction mixture was diluted with H_2O (10 mL), extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude intermediate **11B** (120 mg, crude) as a yellow solid. LC-MS (ESI): RT = 1.033 min, mass calc. for $C_{25}H_{17}F_4N_5OS$ 511.11, m/z found 512.2 $[M+H]^+$.

7-fluoro-5-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]-1H-benzotriazole

[00241] A mixture of intermediate **11B** (120 mg, 0.23 mmol, 1 *eq*) in TFA (1 mL) was stirred at 70 °C for 6 hrs. The reaction mixture was concentrated under reduced pressure to give a

residue, which was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 50%-80%, 6.5 min) to afford **Compound 11** (7.7 mg, 8.4% yield) as a white solid. LC-MS (ESI): RT = 0.862 min, mass calc. for $C_{17}H_9F_4N_5S$ 391.05, m/z found 392.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 8.57 (d, *J* = 2.5 Hz, 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 8.09 (s, 1H), 7.79 - 7.74 (m, 2H), 7.73 - 7.67 (m, 2H), 7.56 (d, *J* = 11.0 Hz, 1H).

Example 12: 6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (Compound 12)



6-bromo-3-(4-methoxybenzyl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00242] To a solution of 6-bromo-3H-triazolo[4,5-b]pyridine (**12A**, 100 mg, 0.50 mmol, 1 *eq*) and PMBCl (94.4 mg, 0.60 mmol, 82 uL, 1.2 *eq*) in DMF (2 mL) was added Cs_2CO_3 (327.4 mg, 1.00 mmol, 2 *eq*). The reaction mixture was stirred at 25 °C for 6 hrs. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~30% Ethyl acetate/Petroleum ethergradient @ 20 mL/min) to give intermediate **12B** (91 mg, 0.24 mmol, 48.2% yield) as a gray solid.

3-(4-methoxybenzyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00243] A mixture of intermediate **12B** (90 mg, 0.28 mmol, 1 *eq*), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (**6C**, 107.4 mg, 0.42 mmol, 1.5 *eq*), KOAc (55.3 mg, 0.56 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (20.6 mg, 28.2 umol, 0.1 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give crude intermediate **12C** (100 mg, crude) as black oil, which use in the next step without further purification.

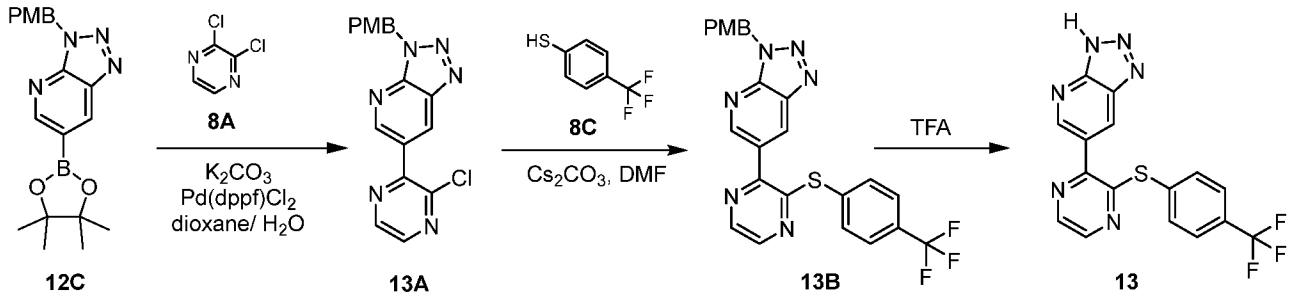
3-(4-methoxybenzyl)-6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00244] A mixture of 2-chloro-3-[4-(trifluoromethyl)phenoxy]pyrazine (**7A**, 70 mg, 0.25 mmol, 1 *eq*), intermediate **12C** (100 mg, 0.27 mmol, 1.07 *eq*), K_2CO_3 (70.4 mg, 0.50 mumol, 2 *eq*) and $Pd(dppf)Cl_2$ (18.6 mg, 25.4 umol, 0.1 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ethergradient @ 25 mL/min) to give intermediate **12D** (55 mg, 83.9 umol, 32.9% yield) as a brown oil.

6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00245] A mixture of intermediate **12D** (45 mg, 94.0 umol, 1 *eq*) in TFA (2 mL) was stirred at 70 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove part of TFA. Then the residue was diluted with H_2O (5 mL) and neutralized to pH = 7~8 with 2M NaOH, then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um;mobile phase: [water(0.05%HCl)-ACN];B%: 35%-65%,8.5min) to afford **Compound 12** (4.6 mg, 13.4% yield) as a white solid. LC-MS (ESI): RT = 0.785 min, mass calcd for $C_{16}H_9F_3N_6O$ 358.28 m/z found 359.0$[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 9.47 (d, *J* = 2.0 Hz, 1H), 9.11 (d, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.5 Hz, 1H), 8.19 (d, *J* = 2.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H).

Example 13: 6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3*H*-[1,2,3]triazolo[4,5-*b*]pyridine (Compound 13)



6-(3-chloropyrazin-2-yl)-3-(4-methoxybenzyl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00246] A mixture of 2,3-dichloropyrazine (**8A**, 90 mg, 0.60 mmol, 1 *eq*) , intermediate **12C** (221.2 mg, 0.60 mmol, 1 *eq*) , K_2CO_3 (166.9 mg, 1.21 mmol, 2 *eq*)and Pd(dppf)Cl_2 (22.1 mg, 30.2 umol, 0.05 *eq*) in dioxane (4 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 30 mL/min) to give intermediate **13A** (125 mg, 0.26 mmol, 44.5% yield) as a yellow oil.

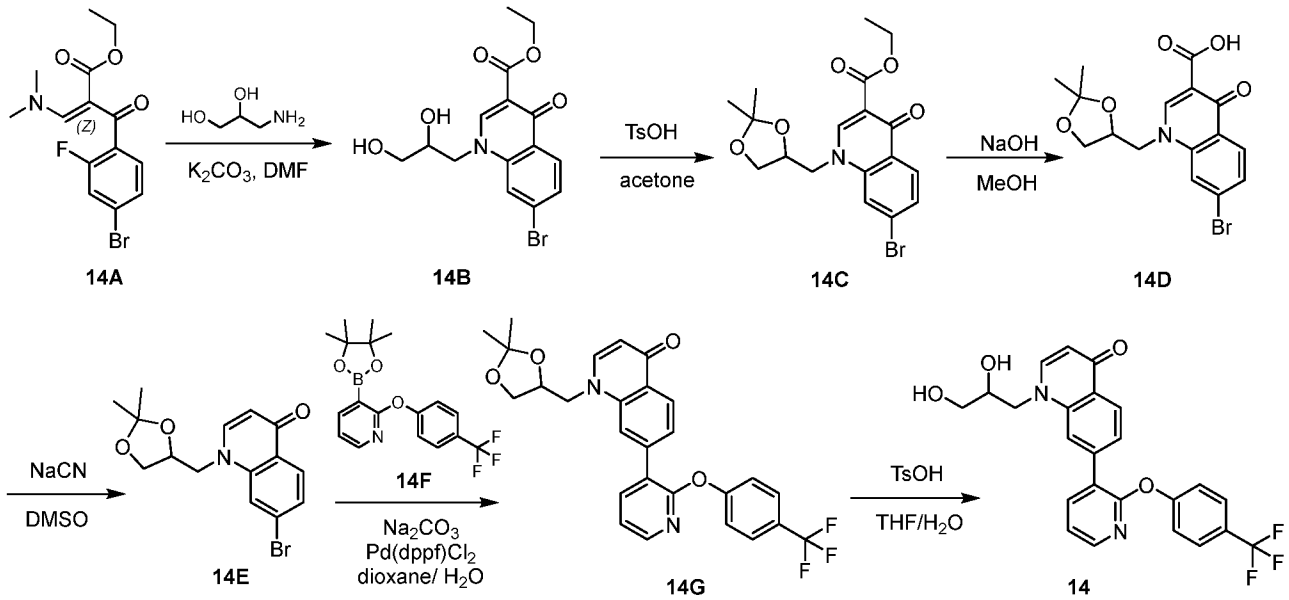
3-(4-methoxybenzyl)-6-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00247] To a solution of intermediate **13A** (125 mg, 0.35 mmol, 1 *eq*) in DMF (3 mL) was added Cs_2CO_3 (230.9 mg, 0.70 mmol, 2 *eq*) and 4-(trifluoromethyl)benzenethiol (**8C**, 63.1 mg, 0.35 mmol, 1 *eq*). The reaction mixture was stirred at 100 °C for 2 hrs. The reaction mixture was added H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ethergradient @ 25 mL/min) to give intermediate **13B** (90 mg, 0.13 mmol, 36.9% yield) as a yellow oil.

6-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine

[00248] A mixture of intermediate **13B** (80 mg, 0.16 mmol, 1 *eq*) in TFA (2 mL) was stirred at 70 °C for 3 hrs. The reaction mixture was concentrated under reduced pressure to remove TFA. Then the residue was diluted with H_2O (5 mL) and neutralized to pH = 7~8with 2M NaOH, then extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um;mobile phase: [water(0.05%HCl)-ACN];B%: 30%-60%,8.5min) to afford **Compound 13** (9.1 mg, 14.6% yield) as a white solid. LC-MS (ESI): RT = 0.855 min, mass calcd for $C_{16}H_9F_3N_6S$ 374.34 m/z found 375.2$[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 9.02 (d, J = 2.0 Hz, 1H), 8.85 (br s, 1H), 8.64 (d, J = 2.3 Hz, 1H), 8.53 (d, J = 2.5 Hz, 1H), 7.79 - 7.73 (m, 2H), 7.72 - 7.67 (m, 2H).

Example 14: 1-(2,3-Dihydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1*H*)-one (Compound 14)



Ethyl 7-bromo-1-(2,3-dihydroxypropyl)-4-oxo-quinoline-3-carboxylate

[00249] To a solution of ethyl (*Z*)-2-(4-bromo-2-fluorobenzoyl)-3-(dimethylamino)acrylate (**14A**, 800 mg, 2.32 mmol, 1 *eq*) and 3-aminopropane-1,2-diol (211.7 mg, 2.32 mmol, 0.18 mL, 1 *eq*) in DMF (10 mL) was added K_2CO_3 (803.1 mg, 5.81 mmol, 2.5 *eq*). The reaction mixture was stirred at 90 °C for 2 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum to give crude intermediate **14B** (880 mg, crude) as a yellow oil, which was used for the next step directly without further purification.

Ethyl 7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-oxo-quinoline-3-carboxylate ;

[00250] To a solution of intermediate **14B** (780 mg, 2.11 mmol, 1 *eq*) in acetone (10 mL) was added TsOH (36.2 mg, 0.21 mmol, 0.1 *eq*). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~90% Ethyl acetate/Petroleum ether gradient @35 mL/min) to give intermediate **14C** (290 mg, 0.65 mmol, 30.8% yield) as a yellow oil. LC-MS (ESI): RT = 1.050 min, mass calcd. For $C_{18}H_{20}BrNO_5$, 409.05 m/z found 410.0 $[M+H]^+$.

7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-oxo-quinoline-3-carboxylic acid;

[00251] To a solution of intermediate **14C** (290 mg, 0.71 mmol, 1 eq) in MeOH (4 mL) was added NaOH (2 M, 1.77 mL, 5 eq). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was concentrated in vacuum. The residue was adjusted pH = 6 with 1M HCl (aq). The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with H_2O (10 mL), brine (10 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **14D** (245 mg, 0.62 mmol, 87.9% yield) as a yellow solid, which was used for the next step directly without further purification. LC-MS (ESI): RT = 0.912 min, mass calcd. For $C_{16}H_{16}BrNO_5$, 381.02 m/z found 383.8 $[M+H]^+$.

7-bromo-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]quinolin-4-one;

[00252] To a solution of intermediate **14D** (245 mg, 0.64 mmol, 1 *eq*) in DMSO (5 mL) was added NaCN (251.3 mg, 5.13 mmol, 8 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 120 °C for 20 hrs. The reaction mixture was poured into ice water (10 mL), extracted with EtOAc (20 mL x 3). The combined organic phase was washed with H_2O (5 ml), brine (5 mL) and dried over Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **14E** (150 mg, 0.39 mmol, 61.5% yield) as a yellow oil, which was used for the next step directly without further purification. LC-MS (ESI): RT = 0.720 min, mass calcd. For $C_{15}H_{16}BrNO_3$, 337.03 m/z found 339.8 $[M+H]^+$.

1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-7-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]quinolin-4-one;

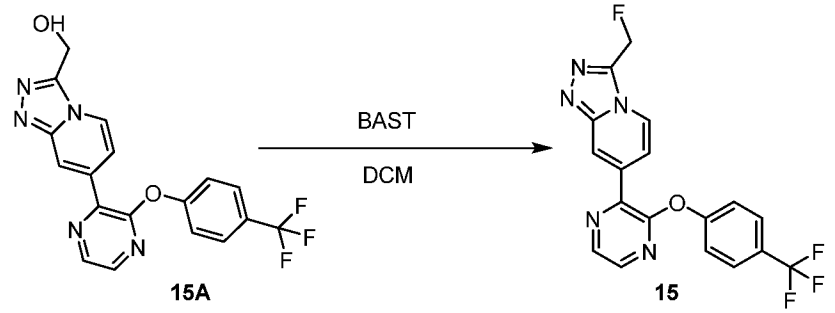
[00253] To a solution of intermediate **14E** (80 mg, 0.24 mmol, 1 *eq*) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl)phenoxy)pyridine (**14F**, 103.6 mg, 0.28 mmol, 1.2 *eq*) in dioxane (2 mL) and H_2O (0.2 mL) were added Pd(dppf)Cl_2 (17.3 mg, 23.6 umol,

0.1 *eq*) and Na_2CO_3 (50.1 mg, 0.47 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 2 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~5% DCM/MeOH @ 30 mL/min) to give intermediate **14G** (86 mg, 0.16 mmol, 68.8% yield) as a gray solid. LC-MS (ESI): RT = 0.839 min, mass calcd. For $C_{27}H_{23}F_3N_2O_4$, 496.16 m/z found 497.1 $[M+H]^+$.

1-(2,3-dihydroxypropyl)-7-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]quinolin-4-one;

[00254] To a solution of intermediate **14G** (76 mg, 0.15 mmol, 1 *eq*) in THF (2 mL) and H_2O (1 mL) was added TsOH (263.6 mg, 1.53 mmol, 10 *eq*). The reaction mixture was stirred at 60 °C for 2 hrs. The reaction mixture was concentrated in vacuum and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 20%-50%, 6.5 min) to afford **Compound 14** (48 mg, 68.7% yield) as a white solid. LC-MS (ESI): RT = 0.738 min, mass calcd. For $C_{24}H_{19}F_3N_2O_4$, 456.13 m/z found 457.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.37 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 7.5 Hz, 1H), 8.27 (s, 1H), 8.25 (dd, *J* = 1.7, 4.8 Hz, 1H), 8.16 (dd, *J* = 1.8, 7.4 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.46 - 7.38 (m, 3H), 6.62 (br d, *J* = 7.4 Hz, 1H), 4.83 (br d, *J* = 12.1 Hz, 1H), 4.20 - 4.16 (m, 3H), 3.89 (br d, *J* = 5.3 Hz, 1H), 3.53 - 3.46 (m, 1H), 3.38 (dd, *J* = 6.5, 10.9 Hz, 1H).

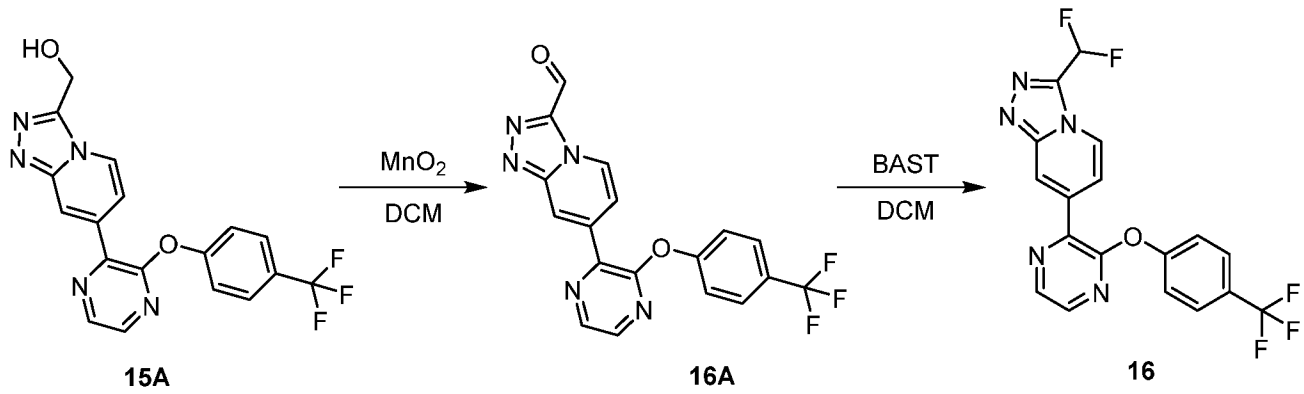
Example 15: 3-(Fluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (Compound 15)



[00255] To a solution of (7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol (**15A**, 40 mg, 0.10 mmol, 1 *eq*) in DCM (2 mL) was added dropwise 2-methoxy-N-(2-methoxyethyl)-N-(trifluoro-sulfanyl)ethanamine (BAST, 34.3 mg, 0.15 mmol, 33.9 uL, 1.5 *eq*) at 0°C under N_2. After addition, the mixture was stirred at 0°C for 2 hrs. The residue was poured into H_2O (30 mL) at 0°C and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum and purified by Prep-HPLC (column:

3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 35%-65%, 6.5min) to afford **Compound 15** (5.6 mg, 14.4 umol, 13.9% yield, 100% purity) as a white solid. LC-MS (ESI): RT = 0.792 min, mass calcd for $C_{18}H_{11}F_4N_5O$ 389.09, m/z found 389.9 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 9.01 - 8.90 (m, 2H), 8.61 (d, *J* = 2.5 Hz, 1H), 8.42 (d, *J* = 7.3 Hz, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 6.16 (s, 1H), 6.04 (s, 1H).

Example 16: 3-(Difluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (Compound 16)



15A 16A 16

7-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-[1,2,4]triazolo[4,3-a]pyridine-3-carbaldehyde

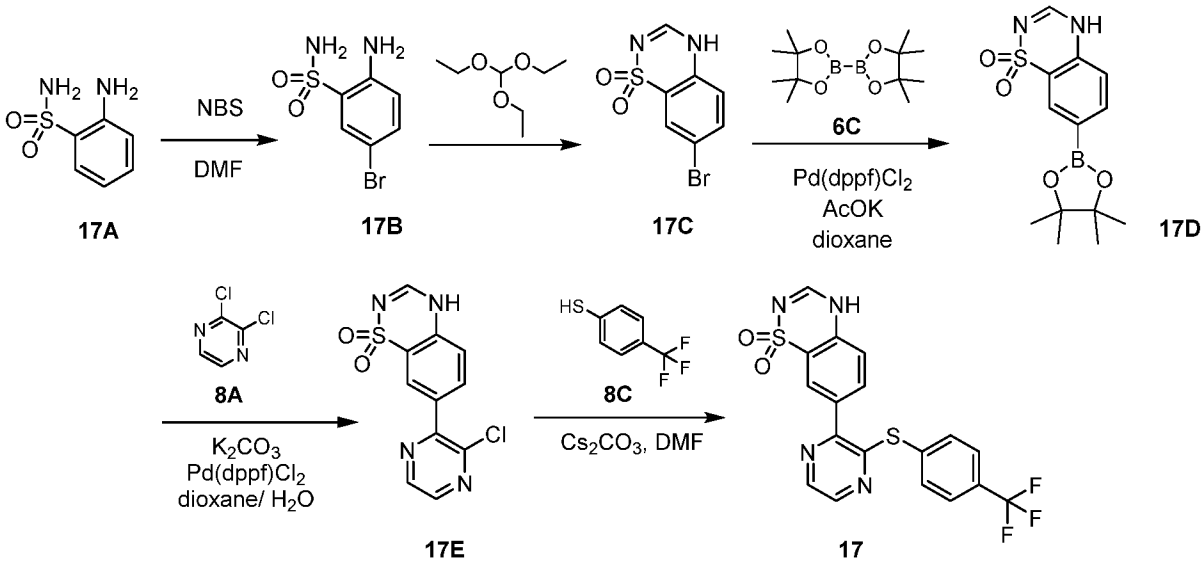
[00256] To a solution of **15A** (75 mg, 0.19 mmol, 1 *eq*) in DCM (2 mL) was added MnO_2 (84.2 mg, 0.97 mmol, 5 *eq*). The reaction mixture was stirred at 20 °C for 16 hrs. The reaction mixture was filtered, and the filter cake was washed with EtOAc (15 mL x 2). The filtrate was concentrated in vacuum to give crude intermediate **16A** (67 mg, crude) as a yellow solid, which was used for next step without further purification.

3-(difluoromethyl)-7-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]-[1,2,4]triazolo[4,3-a]pyridine

[00257] To a solution of intermediate **16A** (58 mg, 0.15 mmol, 1 *eq*) in DCM (1 mL) was added BAST (166.5 mg, 0.75 mmol, 0.16 mL, 5 *eq*) at 0°C under N_2. After addition, the mixture was stirred at 0 °C for 1 hr. The residue was poured into H_2O (30 mL) at 0°C and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by Prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 40%-70%, 6.5min) to afford **Compound 16** (6.4 mg, 10.2% yield) as a white solid. LC-MS (ESI): RT = 0.828 min, mass calcd for $C_{18}H_{10}F_5N_5O$ 407.08, m/z found 408.2 $[M+H]^+$; ^1H NMR (400 MHz, CD_3OD) δ 8.80 (s, 1H), 8.70 (d, *J* = 7.3 Hz,

1H), 8.55 (d, *J* = 2.3 Hz, 1H), 8.22 (d, *J* = 2.5 Hz, 1H), 8.10 (d, *J* = 7.3 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.65 - 7.34 (m, 3H).

Example 17: 7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (Compound 17)



2-amino-5-bromo-benzenesulfonamide

[00258] To a solution of 2-aminobenzenesulfonamide (**17A**, 5 g, 29.04 mmol, 1 *eq*) in DMF (40 mL) was added NBS (5.17 g, 29.04 mmol, 1 *eq*). The reaction mixture was stirred at 20 °C for 2 hrs. The residue was poured into H_2O (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc(50 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude product. The crude product was triturated with (PE/EtOAc = 10/1, 30 mL) at 20 °C for 1 hr to give intermediate **17B** (6.1 g, 24.29 mmol, 83.7% yield) as a black brown solid.

7-bromo-4H-1λ⁶,2,4-benzothiadiazine 1,1-dioxide

[00259] To a solution of intermediate **17B** (3 g, 11.95 mmol, 1 *eq*) in triethoxymethane (26.73 g, 180.36 mmol, 30 mL, 15.1 *eq*) was stirred at 110 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure to remove solvent to give crude product. The crude product was triturated with (PE/EtOAc = 10/1, 30 mL) at 20°C for 1hr to give intermediate **17C** (2.8 g, 10.72 mmol, 89.8% yield) as a black brown solid.

7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide

[00260] A mixture of intermediate **17C** (1 g, 3.83 mmol, 1 *eq*), **6C** (1.46 g, 5.75 mmol, 1.5 *eq*), Pd(dppf)Cl2 (280.3 mg, 0.38 mmol, 0.1 *eq*), KOAc (563.8 mg, 5.75 mmol, 1.5 *eq*) in dioxane

(12 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture containing intermediate **17D** was used directely for the next step.

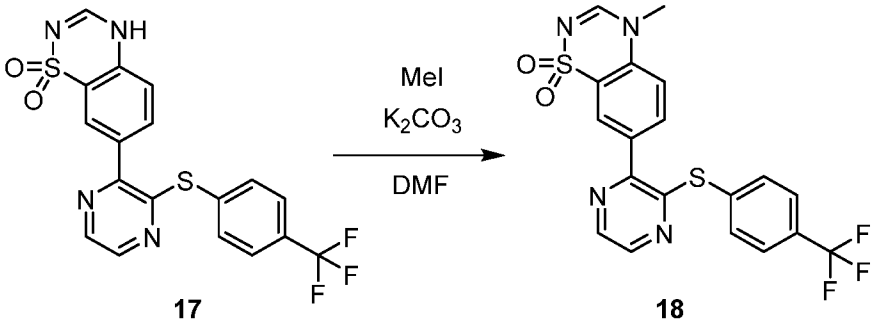
7-(3-chloropyrazin-2-yl)-4H-1λ⁶,2,4-benzothiadiazine 1,1-dioxide

[00261] 2,3-Dichloropyrazine (**8A**, 688.3 mg, 4.62 mmol, 1.1 *eq*), $Pd(dppf)Cl_2$ (234.2 mg, 0.32 mmol, 0.1 *eq*), K_2CO_3 (663.4 mg, 4.80 mmol, 1.5 *eq*) and H_2O (3 mL) were added to the reaction mixture containing intermediate **17D** (1 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 hrs under N_2 atmosphere. The residue was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by flash chromatography on silica gel (20 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~50%) to give intermediate **17E** (0.65 g, 2.21 mmol, 68.9% yield) as a black brown solid.

7-[3-[4-(trifluoromethyl)phenyl]sulfanylpyrazin-2-yl]-4H-1λ⁶,2,4-benzothiadiazine 1,1-dioxide

[00262] To a solution of intermediate **17E** (75 mg, 0.25 mmol, 1 *eq*) in DMF (1.5 mL) were added K2CO3 (70.3 mg, 0.51 mmol, 2 *eq*) and 4-(trifluoromethyl)benzenethiol (**8C**, 49.9 mg, 0.28 mmol, 1.1 *eq*). The reaction mixture was stirred at 100 °C for 3 hrs. The residue was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by Prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 35%-65%, 6.5min) to afford **Compound 17** (38.4 mg, 31.3% yield, HCl) as a white solid. LC-MS (ESI): RT = 0.790 min, mass calcd for $C_{18}H_{11}F_3N_4O_2S_2$ 436.03, m/z found 436.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ12.54 (s, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 8.45 (d, *J* = 2.5 Hz, 1H), 8.17 (d, *J* = 2.0 Hz, 1H), 8.11 - 8.03 (m, 2H), 7.79 - 7.74 (m, 2H), 7.74 - 7.69 (m, 2H), 7.49 (d, *J* = 8.5 Hz, 1H).

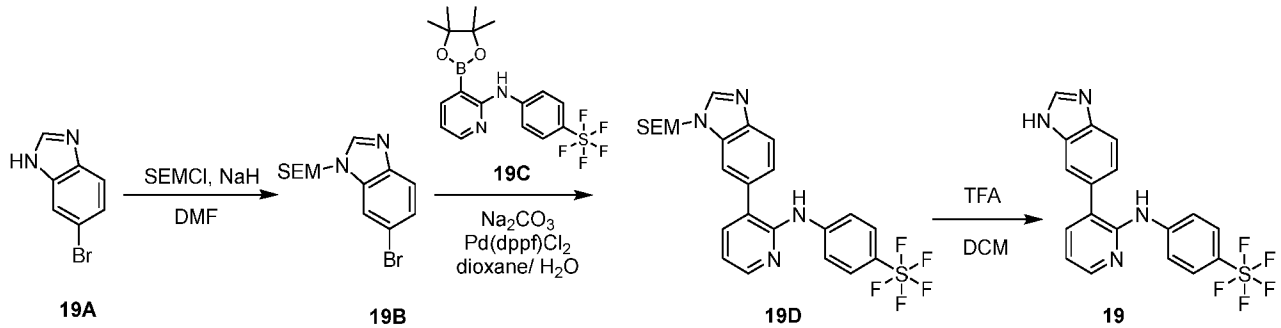
Example 18: 4-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide (Compound 18)



17 18

[00263] To a solution of **Compound 17** (75 mg, 0.17 mmol, 1 *eq*) in DMF (1 mL) was added CH_3I (36.6 mg, 0.26 mmol, 16.1 uL, 1.5 *eq*) and K_2CO_3 (35.6 mg, 0.26 mmol, 1.5 *eq*). The reaction mixture was stirred at 20 °C for 3 hrs. The reaction mixture was quenched by addition H_2O (30 mL), and then diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by Prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water (0.04%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 41%-71%, 7.8min) to afford **Compound 18** (31.3 mg, 39.6% yield) as a white solid. LC-MS (ESI): RT = 0.812 min, mass calcd for $C_{19}H_{13}F_3N_4O_2S_2$ 450.04, m/z found 450.9 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, *J* = 2.5 Hz, 1H), 8.48 (d, *J* = 2.5 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 8.21 - 8.14 (m, 2H), 7.81 - 7.75 (m, 2H), 7.75 - 7.66 (m, 3H), 3.70 (s, 3H).

Example 19: 3-(1*H*-Benzo[*d*]imidazol-6-yl)-*N*-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 19)



19A 19B 19D 19

2-[(6-bromobenzimidazol-1-yl)methoxy]ethyl-trimethyl-silane

[00264] To a solution of 6-bromo-1*H*-benzimidazole (**19A**, 200 mg, 1.02 mmol, 1 *eq*) in DMF (3 mL) was added NaH (48.7 mg, 1.22 mmol, 60%, 1.2 *eq*) at 0°C, then the reaction was allowed to warm up to 25 °C and stirred for 0.5 hour. The reaction mixture was cooled to 0 °C, and then 2-(chloromethoxy)ethyl-trimethyl-silane (SEMCl, 220.0 mg, 1.32 mmol, 0.23 mL, 1.3 *eq*) was

added. The reaction mixture was allowed to warm up to 25 °C and stirred for 2 hrs. The mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (6 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure to give crude intermediate **19B** (213 mg, crude) as a yellow oil, which was used in the next step without further purification.

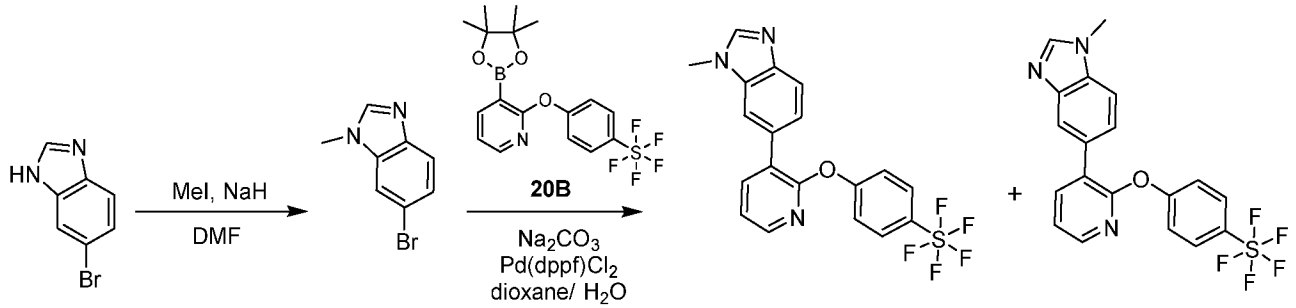
***N*-[4-(pentafluoro-sulfanyl)phenyl]-3-[3-(2-trimethylsilylethoxymethyl)benzimidazol-5-yl]pyridin-2-amine**

[00265] To a solution of intermediate **19B** (77.5 mg, 0.23 mmol, 1 *eq*) and N-[4-(pentafluoro-sulfanyl)phenyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (**19C**, 100 mg, 0.23 mmol, 1 *eq*) in dioxane (1 mL) and H_2O (0.2 mL) was added Na_2CO_3 (50.2 mg, 0.47 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (8.6 mg, 11.8 umol, 0.05 *eq*). The reaction mixture was stirred at 90 °C for 4 hrs. The mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (6 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Petroleum ether/Ethyl acetate gradient @ 30 mL/min) to give intermediate **19D** (105 mg, 93.6 umol, 39.5% yield) as a yellow solid.

3-(3*H*-benzimidazol-5-yl)-*N*-[4-(pentafluoro-sulfanyl)phenyl]pyridin-2-amine

[00266] A solution of intermediate **19D** (105 mg, 0.19 mmol, 1 *eq*) in TFA (2 mL) and DCM (1 mL). The reaction mixture was stirred at 25 °C for 16 hrs. The reaction mixture was concentrated under reduce pressure. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 20%-50%, 6.5 min) to afford **Compound 19** (30.2 mg, 34.8% yield, HCl) as a white solid. LC-MS (ESI): RT = 0.796 min, mass calcd for $C_{18}H_{13}F_5N_4S$ 412.08 m/z, found 413.1 $[M+H]^+$, ^1H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.50 (s, 1H), 8.31 (dd, J = 1.6, 4.6 Hz, 1H), 7.98 - 7.91 (m, 2H), 7.74 - 7.68 (m, 3H), 7.68 - 7.63 (m, 3H), 7.14 (dd, J = 4.9, 7.4 Hz, 1H).

Example 20: 1-Methyl-6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 20) and 1-methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 20a)



6-bromo-1-methyl-benzimidazole

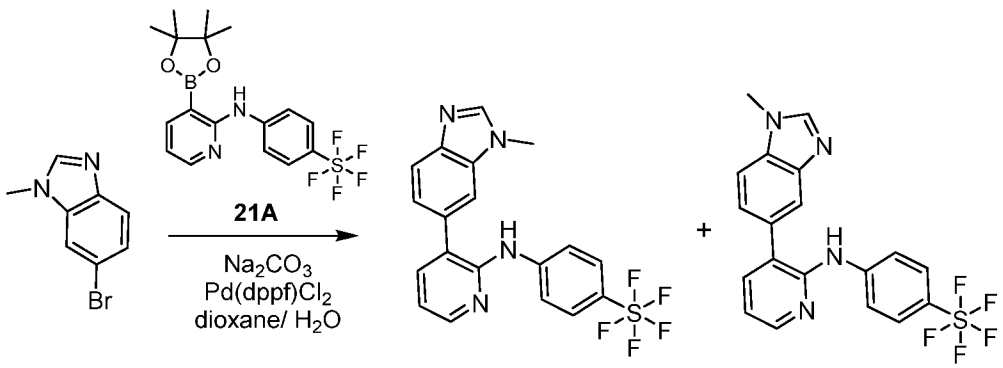
[00267] To a solution of 6-bromo-1*H*-benzimidazole (**19A**, 300 mg, 1.52 mmol, 1 *eq*) in DMF (3 mL) was added NaH (73.0 mg, 1.83 mmol, 60%, 1.2 *eq*) at 0°C, then the reaction mixture was allowed to warm up to 25 °C and stirred for 0.5 hr. The reaction mixture was cooled to 0 °C, and then MeI (259.3 mg, 1.83 mmol, 113.74 uL, 1.2 *eq*) was added. The reaction mixture was allowed to warm up to 25 °C and stirred for 2 hours. The reaction mixture was quenched with H_2O (15 mL). The mixture was diluted with water (10 mL) and the resultant mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um;mobile phase: [water(0.05%HCl)-ACN];B%: 0%-25%,8.5min) to give crude intermediate **20A** (89 mg, crude) as a white solid.

[00268] To a solution of intermediate **20A** (80 mg, 0.37 mmol, 1 *eq*) and pentafluoro-[4-[[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]phenyl]-sulfane (**20B**, 192.5 mg, 0.45 mmol, 1.2 *eq*) in dioxane (1 mL) and H_2O (0.2 mL) was added Na_2CO_3 (80.3 mg, 0.75 mmol, 2 *eq*) and Pd(dppf)Cl_2 (13.8 mg, 18.9 umol, 0.05 *eq*). The reaction mixture was stirred at 90 °C for 4 hrs. The reaction mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (8 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~100% Petroleum ether/Ethyl acetate gradient @ 30 mL/min) to give the product as a brown oil, which was further purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water (0.04%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 47%-77%, 7.8min) to afford **Compound 20** and **Compound 20a** in a solid mixture. The solid mixture was further purified by SFC(column: DAICEL CHIRALPAK AD(250mm x 30mm,10um);mobile phase: [0.1%NH_3H_2O ETOH]; B%: 35%-35%, min) to give **Compound 20** (5.6 mg, 3.45% yield) as a white solid and **Compound 20a** (11.5 mg, 7.11% yield) as a white solid.

[00269] **Compound 20:** LC-MS (ESI): RT = 0.827 min, mass calcd for $C_{19}H_{14}F_5N_3OS$ 427.39 m/z, found 428.1 $[M+H]^+$, ^1H NMR (400MHz, CD_3OD) δ 8.21 - 8.15 (m, 2H), 8.05 (dd, *J* = 1.9, 7.4 Hz, 1H), 7.83 (s, 1H), 7.80 (d, *J* = 4.3 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.35 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.22 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H)

[00270] **Compound 20a:** LC-MS (ESI): RT = 0.827 min, mass calcd for $C_{19}H_{14}F_5N_3OS$ 427.39 m/z, found 428.1 $[M+H]^+$, ^1H NMR (400MHz, CD_3OD) δ 8.22 - 8.14 (m, 2H), 8.02 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.90 (s, 1H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.66 - 7.57 (m, 2H), 7.35 (dd, *J* = 4.9, 7.4 Hz, 1H), 7.20 (d, *J* = 9.0 Hz, 2H), 3.93 (s, 3H).

Example 21: 3-(1-Methyl-1*H*-benzo[*d*]imidazol-6-yl)-*N*-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 21) and 3-(1-methyl-1*H*-benzo[*d*]imidazol-5-yl)-*N*-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 21a)



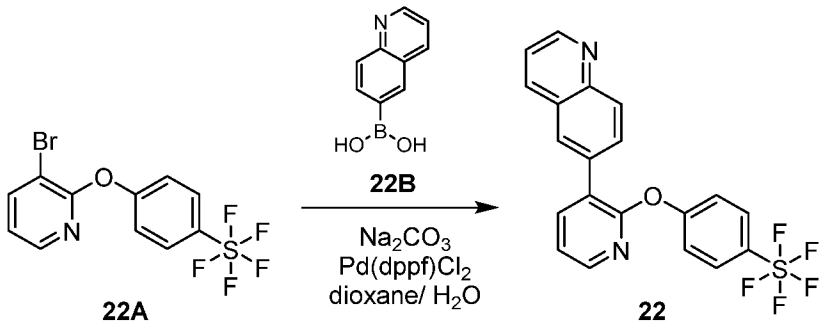
20A **21** **21a**

[00271] To a solution of intermediate **20A** (90 mg, 0.42 mmol, 1 *eq*) and *N*-[4-(pentafluoro-sulfanyl)phenyl]-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine (**21A**, 180 mg, 0.42 mmol, 1 *eq*) in dioxane (1 mL) and H_2O (0.2 mL) was added $Pd(dppf)Cl_2$ (15.6 mg, 21.3 umol, 0.05 *eq*) and Na_2CO_3 (90.3 mg, 0.85 mmol, 2 *eq*). The reaction mixture was stirred at 90 °C for 4 hrs. The reaction mixture was diluted with water (5 mL) and the resultant mixture was extracted with EtOAc (6 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um;mobile phase: [water (0.05%HCl)-ACN]; B%: 10%-40%,8.5 min) to afford **Compound 21** (15.95 mg, 8.06% yield, HCl) as a white solid and **Compound 21a** (15.9 mg, 8.0% yield) as a white solid.

[00272] **Compound 21:** LC-MS (ESI): RT = 0.814 min, mass calcd for $C_{19}H_{15}F_5N_4S$ 426.09 m/z, found 427.1 $[M+H]^+$, ^1H NMR (400 MHz, CD_3OD) δ 8.26 (dd, *J* = 1.6, 4.9 Hz, 1H), 8.20 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.71 - 7.65 (m, 2H), 7.64 - 7.56 (m, 4H), 7.39 (d, *J* = 7.0 Hz, 1H), 7.07 (dd, *J* = 5.0, 7.5 Hz, 1H), 3.92 (s, 3H).

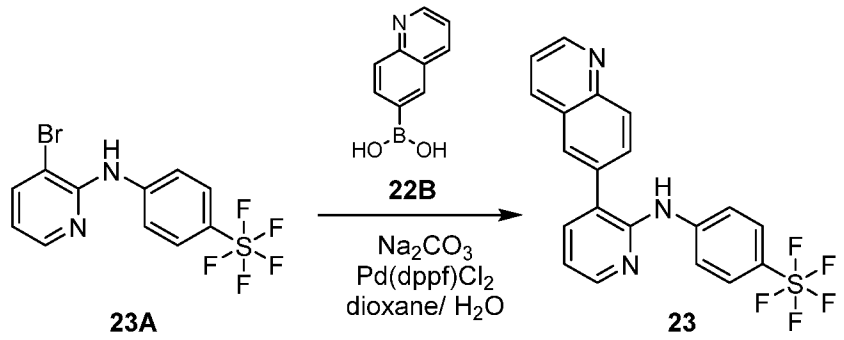
[00273] **Compound 21a:** LC-MS (ESI): RT = 0.813 min, mass calcd for $C_{19}H_{15}F_5N_4S$ 426.09 m/z, found 427.1$[M+H]^+$, ^{1}H NMR (400MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.61 (s, 1H), 8.31 (br d, J = 3.4 Hz, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.97 (s, 1H), 7.78 - 7.68 (m, 4H), 7.67 - 7.61 (m, 2H), 7.16 (dd, J = 5.1, 7.3 Hz, 1H), 4.13 (s, 3H).

Example 22: 6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinoline (Compound 22)



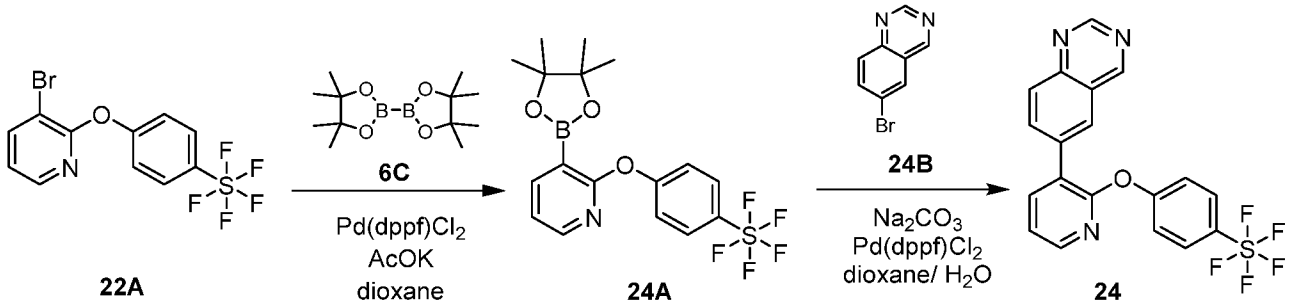
[00274] To a solution of 3-bromo-2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridine (**22A**, 50 mg, 0.13 mmol, 1 *eq*) and quinolin-6-ylboronic acid (**22B**, 27.5 mg, 0.16 mmol, 1.2 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) were added Na_2CO_3 (28.1 mg, 0.26 mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (9.7 mg, 13.2 umol, 0.1 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 2 hrs. The reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc (20 mL), filtered and the filtrated was concentrated in vacuum and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um;mobile phase: [water(0.05%HCl)-ACN]; B%: 35%-65%,6.5min) to afford **Compound 22** (15.4 mg, 27.08% yield) as a gray solid. LC-MS (ESI): RT = 0.781 min, mass calcd. For $C_{20}H_{13}F_5N_2OS$, 424.07 m/z found 424.9 $[M+H]^+$. ^{1}H NMR (500 MHz, CD_3OD) δ 9.36 - 9.23 (m, 2H), 8.67 (d, J = 1.4 Hz, 1H), 8.55 (dd, J = 1.6, 8.9 Hz, 1H), 8.37 (d, J = 9.0 Hz, 1H), 8.28 (dd, J = 1.7, 4.9 Hz, 1H), 8.23 - 8.13 (m, 2H), 7.92 - 7.76 (m, 2H), 7.42 (dd, J = 4.9, 7.5 Hz, 1H), 7.32 (d, J = 8.9 Hz, 2H).

Example 23: *N*-(4-(Pentafluoro-λ6-sulfaneyl)phenyl)-3-(quinolin-6-yl)pyridin-2-amine (Compound 23)



[00275] To a solution of 3-bromo-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine (**23A**, 50 mg, 0.13 mmol, 1 eq) and quinolin-6-ylboronic acid (**22B**, 27.6 mg, 0.16 mmol, 1.2 eq) in dioxane (1 mL) and H_2O (0.1 mL) were added Na_2CO_3 (28.2 mg, 0.26 mmol, 2 eq) and $Pd(dppf)Cl_2$ (9.7 mg, 13.3 umol, 0.1 eq). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 16 hrs. The reaction mixture was concentrated in vacuum. The residue was diluted with EtOAc (20 mL), filtered and the filtrated was concentrated in vacuum and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 40%-70%,6.5min) to afford **Compound 23** (28.4 mg, 50.3% yield) as a yellow solid. LC-MS (ESI): RT = 0.766 min, mass calcd. For $C_{20}H_{13}F_5N_3S$, 423.08 m/z found 423.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.35 (d, *J* = 6.5 Hz, 2H), 8.67 (s, 1H), 8.47 - 8.42 (m, 1H), 8.41 - 8.36 (m, 1H), 8.33 (d, *J* = 6.3 Hz, 1H), 8.27 - 8.19 (m, 1H), 8.17 - 8.11 (m, 1H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.60 (br d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 6.8 Hz, 1H).

Example 24: 6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinazoline (Compound 24)



pentafluoro-[4-[[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-pyridyl]oxy]phenyl]-sulfane

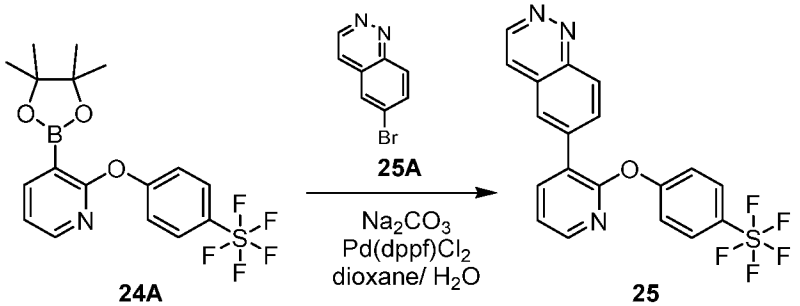
[00276] To a solution of **22A** (80 mg, 0.21 mmol, 1 *eq*) and **6C** (54.0 mg, 0.21 mmol, 1 *eq*) in dioxane (2 mL) were added $Pd(dppf)Cl_2$ (15.6 mg, 21.3 umol, 0.1 *eq*) and AcOK (41.8 mg, 0.43 mmol, 2 *eq*) . The suspension was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 100°C for 3 hrs under N_2. The reaction mixture was concentrated

under reduced pressure to give crude intermediate **24A** (90 mg, crude, in dioxane, black oil) was used in the next step without further purification.

pentafluoro-[4-[(3-quinazolin-6-yl-2-pyridyl)oxy]phenyl]-sulfane

[00277] To a mixture of intermediate **24A** (90 mg, 0.21 mmol, 1 *eq*) and 6-bromoquinazoline (**24B**, 44.5 mg, 0.21 mmol, 1 *eq*) in dioxane (1 mL) and H_2O (0.25 mL) were added K_2CO_3 (58.8 mg, 0.43mmol, 2 *eq*) and $Pd(dppf)Cl_2$ (15.6 mg, 21.3 umol, 0.1 *eq*). The suspension was degassed under vacuum and purged with N_2 for 3 times. The reaction mixture was stirred at 100°C for 3 hrs under N_2. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water ($0.05\%NH_3H_2O$)-ACN]; B%: 47%-77%, 7.8 min) to afford **Compound 24** (36.8 mg, 39.5% yield) as a white solid. LC-MS (ESI): RT = 2.187 min, mass calc. for $C_{19}H_{12}F_5N_3OS$ 425.06, m/z found 426.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 9.38 (s, 1H), 8.27 (dd, *J* = 1.7, 4.8 Hz, 1H), 8.24 - 8.12 (m, 3H), 7.95 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.30 - 7.23 (m, 3H).

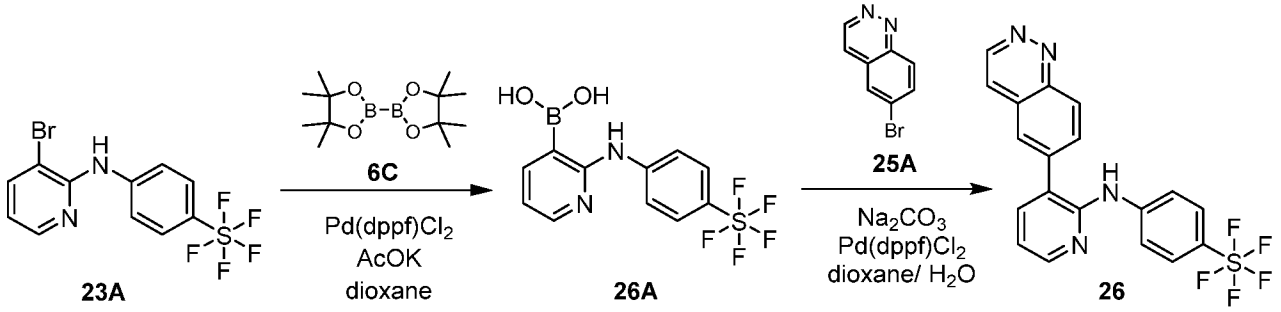
Example 25: 6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)cinnoline (Compound 25)



[00278] To a solution of **24A** (112 mg, 0.26 mmol, 1 eq) and 6-bromocinnoline (**25A**, 55.3 mg, 0.26 mmol, 1 eq) in dioxane (1 mL) and H_2O (0.1 mL) were added $Pd(dppf)Cl_2$ (19.3 mg, 26.4 umol, 0.1 eq) and Na_2CO_3 (56.1 mg, 0.53 mmol, 2 eq). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 1 hr. The reaction mixture was filtered, and the filtrate was concentrated in vacuum and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 40%-70%,8.5min) to afford **Compound 25** (27.7 mg, 23.6% yield) as a yellow oil. LC-MS (ESI): RT = 0.855 min, mass calcd. For $C_{19}H_{12}F_5N_3OS$, 425.06 m/z found 425.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.61 (d, *J* =

6.0 Hz, 1H), 9.18 (d, *J* = 6.0 Hz, 1H), 8.72 (s, 1H), 8.70 (s, 2H), 8.31 (dd, *J* = 1.8, 5.0 Hz, 1H), 8.26 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.92 - 7.86 (m, 2H), 7.44 (dd, *J* = 4.8, 7.5 Hz, 1H), 7.36 (d, *J* = 9.0 Hz, 2H).

Example 26: 3-(Cinnolin-6-yl)-*N*-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 26)



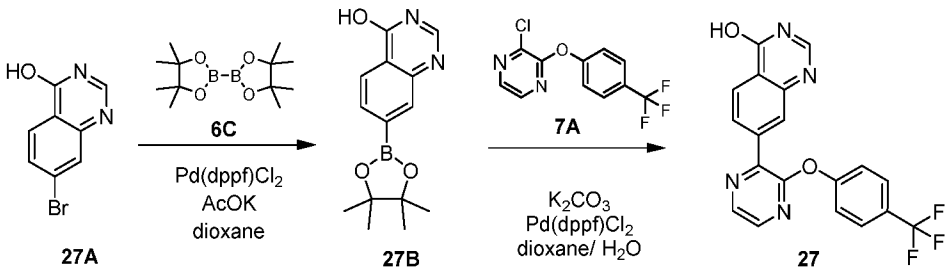
[2-[4-(pentafluoro-sulfanyl)anilino]-3-pyridyl]boronic acid;

[00279] To a solution of **23A** (100 mg, 0.26 mmol, 1 *eq*) and **6C** (81.2 mg, 0.32 mmol, 1.2 *eq*) in dioxane (1 mL) were added $Pd(dppf)Cl_2$ (19.5 mg, 26.6 umol, 0.1 *eq*) and AcOK (52.3 mg, 0.53 mmol, 2 *eq*). The reaction mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 2 hrs. The reaction mixture was filtered, and the filtrate was concentrated in vacuum to give crude intermediate **26A** (90 mg, crude) as a black oil, which was used for the next step directly without further purification.

3-cinnolin-6-yl-N-[4-(pentafluoro-sulfanyl)phenyl]pyridin-2-amine;

[00280] To a solution of intermediate **26A** (90 mg, 0.26 mmol, 1 *eq*) and 6-bromocinnoline (**25A**, 55.3 mg, 0.26 mmol, 1 *eq*) in dioxane (1 mL) and H_2O (0.1 mL) were added $Pd(dppf)Cl_2$ (19.3 mg, 26.4 umol, 0.1 *eq*) and Na_2CO_3 (56.1 mg, 0.53 mmol, 2 *eq*). The mixture was degassed and purged with N_2 for 3 times and stirred at 90 °C for 1 hr. The reaction mixture was filtered, and the filtrate was concentrated in vacuum. The crude product was checked by HPLC and purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water(0.05%HCl)-ACN]; B%: 45%-75%,6.5min) to afford **Compound 26** (2.1 mg, 1.8% yield) as a yellow oil. LC-MS (ESI): RT = 0.842 min, mass calcd. For $C_{19}H_{13}F_5N_4S$, 424.08 m/z found 425.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.53 (br d, *J* = 6.0 Hz, 1H), 8.73 - 8.64 (m, 1H), 8.73 - 8.64 (m, 1H), 8.47 (br s, 1H), 8.34 - 8.15 (m, 3H), 7.89 (br d, *J* = 9.0 Hz, 2H), 7.59 (br d, *J* = 8.8 Hz, 2H), 7.40 (br t, *J* = 6.5 Hz, 1H).

Example 27: 7-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-ol (Compound 27)



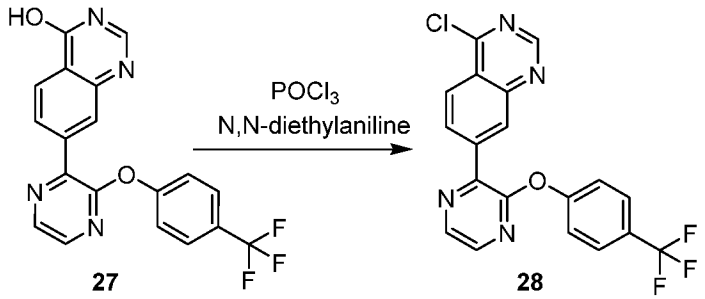
7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-4-ol

[00281] A mixture of 7-bromoquinazolin-4-ol (**27A**, 1 g, 4.44 mmol, 1 *eq*), **6C** (1.3 g, 5.33 mmol, 1.2 *eq*), KOAc (872.1 mg, 8.89 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (162.5 mg, 0.22 mmol, 0.05 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~80% PE/EtOAc ethergradient @ 35 mL/min) to give intermediate **27B** (774 mg, 2.84 mmol, 64.0% yield) as a yellow solid.

7-[3-[4-(trifluoromethyl)phenoxy]pyrazin-2-yl]quinazolin-4-ol

[00282] A mixture of intermediate **27B** (200 mg, 0.73 mmol, 1.2 eq), **7A** (168.2 mg, 0.61 mmol, 1 eq), K_2CO_3 (169.3 mg, 1.23 mmol, 2 eq), $Pd(dppf)Cl_2$ (22.4 mg, 30.6 umol, 0.05 eq) in dioxane (2 mL) and H_2O (0.4 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 5 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% PE/EtOAc ethergradient @ 30 mL/min) to afford **Compound 27** (107 mg, 0.27 mmol, 45.4% yield) as a white solid. LC-MS (ESI): RT = 0.846 min, mass calcd for $C_{19}H_{11}F_3N_4O_2$ 384.31 m/z found 385.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 2.5 Hz, 1H), 8.42 (d, J = 1.1 Hz, 1H), 8.33 - 8.23 (m, 4H), 7.85 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H).

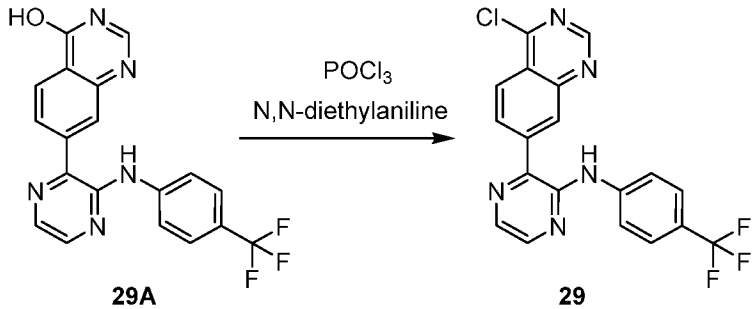
Example 28: 4-Chloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline (Compound 28)



27 28

[00283] To a solution of **Compound 27** (30 mg, 78.0 umol, 1 *eq*) was added $POCl_3$ (825.0 mg, 5.38 mmol, 0.5 mL, 68.9 *eq*) and N,N-diethylaniline (27.9 mg, 0.18 mmol, 29.9 uL, 2.4 *eq*). The reaction mixture was stirred at 100 °C for 4 hrs. After cooling, the reaction mixture was evaporated and the mixture was diluted with H_2O and $CHCl_3$, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% PE/EtOAc ethergradient @ 25 mL/min) to afford **Compound 28** (1.70 mg, 5.3% yield) as a light yellow solid. LC-MS (ESI): RT = 1.013 min, mass calcd for $C_{19}H_{10}ClF_3N_4O$ 402.76 m/z found 403.1 $[M+H]^+$. ^1H NMR (400 MHz, $COCl_3$) δ 9.11 (s, 1H), 8.96 (s, 1H), 8.61 - 8.54 (m, 2H), 8.41 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 2.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H).

Example 29: 3-(4-Chloroquinazolin-7-yl)-*N*-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 29)

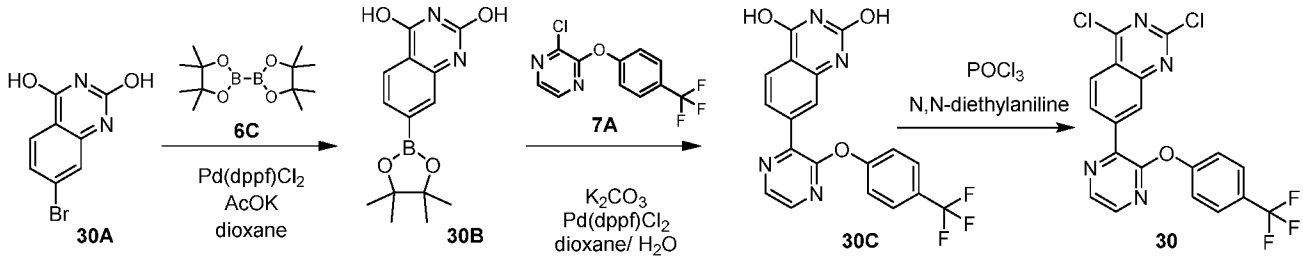


29A 29

[00284] A mixture of 7-(3-((4-(trifluoromethyl)phenyl)amino)pyrazin-2-yl)quinazolin-4-ol (**29A**, 66 mg, 0.17 mmol, 1 *eq*), $POCl_3$ (825.0 mg, 5.38 mmol, 0.5 mL, 31.2 *eq*) and N,N-diethylaniline (61.6 mg, 0.41 mmol, 66.0 uL, 2.4 *eq*) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 4 hrs under N_2 atmosphere. After cooling, the reaction mixture was evaporated, and the mixture was diluted with H_2O (1 mL). The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and

concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash ® Silica Flash Column, Eluent of 0~35% PE/EtOAc ethergradient @ 20 mL/min) to afford **Compound 29** (3.5 mg, 5.0 % yield) as a yellow solid. LC-MS (ESI): RT = 0.978 min, mass calcd for $C_{19}H_{11}ClF_3N_5$ 401.77 m/z found 402.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 8.53 - 8.45 (m, 2H), 8.29 (q, *J* = 2.6 Hz, 2H), 8.13 (dd, *J* = 1.8, 8.6 Hz, 1H), 7.66 - 7.63 (m, 2H), 7.60 - 7.56 (m, 2H), 6.99 (s, 1H).

Example 30: 2,4-dichloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline (Compound 30)



7-(4,4,5,5-Tetramethyl-1,3,2-Dioxaborolan-2-yl)quinazoline-2,4-diol

[00285] A mixture of 7-bromoquinazoline-2,4-diol (**30A**, 1 g, 4.15 mmol, 1 *eq*) , **6C** (1 g, 4.98 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (151.7 mg, 0.20 mmol, 0.05 *eq*), KOAc (814.3 mg, 8.30 mmol, 2 *eq*) in dioxane (10 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 25 g SepaFlash® Silica Flash Column, Eluent of 0~70% PE/EtOAc ethergradient @ 30 mL/min) to give intermediate **30B** (940 mg, 2.25 mmol, 54.2% yield) as a brown solid.

7-[3-[4-(Trifluoromethyl)Phenoxy]pyrazin-2-yl]quinazoline-2,4-diol

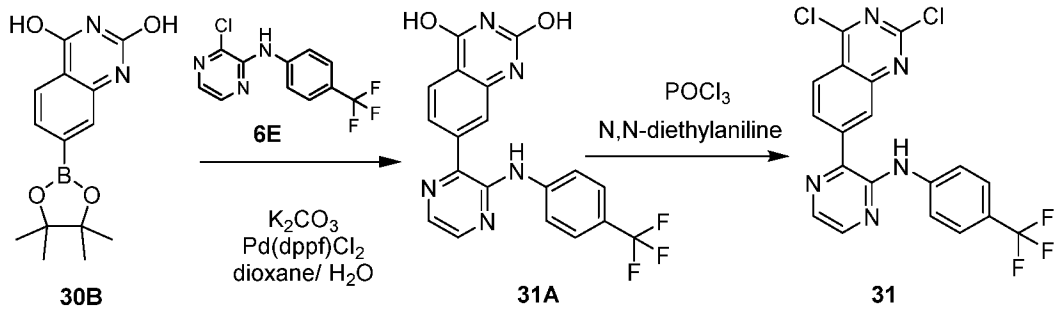
[00286] A mixture of intermediate **30B** (200 mg, 0.47 mmol, 1.2 *eq*), **7A** (109.6 mg, 0.39 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (14.6 mg, 19.9 umol, 0.05 *eq*), K_2CO_3 (110.3 mg, 0.79 mmol, 2 *eq*) in dioxane (2 mL) and H_2O (0.4 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 6 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g

SepaFlash® Silica Flash Column, Eluent of 0~70% PE/EtOAc ethergradient @ 30 mL/min) to give intermediate **30C** (122 mg, 0.30 mmol, 76.3% yield) as a white solid.

2,4-*D*ichloro-7-[3-[4-(Trifluoromethyl)Phenoxy]pyrazin-2-yl]quinazoline

[00287] To a solution of intermediate **30C** (50 mg, 0.12 mmol, 1 *eq*)was added $POCl_3$ (383 mg, 2.5 mmol, 0.23 mL, 20 *eq*) and N,N-Diethylaniline (44.7 mg, 0.29 mmol, 47.9 uL, 2.4 *eq*). The mixture was stirred at 100 °C for 4 hrs. After cooling, the mixture was evaporated, and the mixture was diluted with H_2O and $CHCl_3$. the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um;mobile phase: [water(0.05%HCl)-ACN];B%: 65%-95%,6.5min) to afford **Compound 30** (2.1 mg, 4.0% yield) as a white solid. LC-MS (ESI): RT = 1.022 min, mass calcd for $C_{19}H_9Cl_2F_3N_4O$ 437.20 m/z found 436.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.57 (dd, *J* = 1.5, 8.8 Hz, 1H), 8.49 - 8.44 (m, 1H), 8.34 (d, *J* = 2.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H).

Example 31: 3-(2,4-Dichloroquinazolin-7-yl)-*N*-(4-(trifluoromethyl)phenyl)pyrazin-2-amine (Compound 31)



7-[3-[4-(trifluoromethyl)anilino]pyrazin-2-yl]quinazoline-2,4-diol

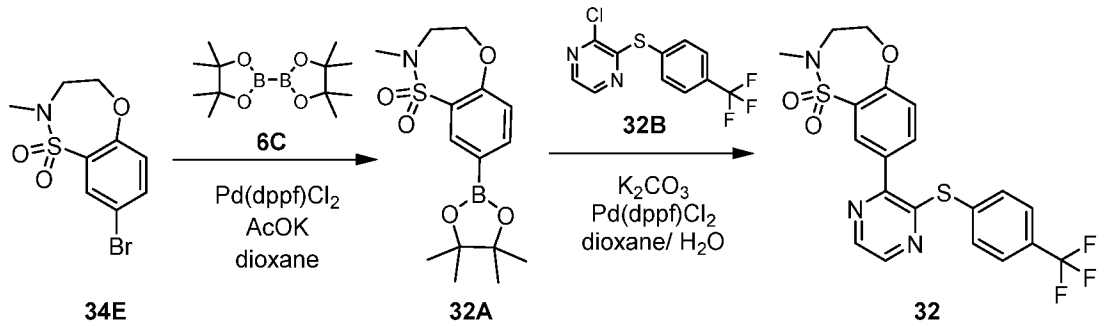
[00288] A mixture of intermediate **30B** (350 mg, 1.21 mmol, 1 *eq*), **6E** (398.91 mg, 1.46 mmol, 1.2 *eq*), K_2CO_3 (335.8 mg, 2.43 mmol, 2 *eq*), $Pd(dppf)Cl_2$ (44.45 mg, 60.7 umol, 0.05 *eq*) in dioxane (3 mL) and H_2O (0.6 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 90 °C for 16 hr under N_2 atmosphere. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 12 g

SepaFlash® Silica Flash Column, Eluent of 0~70% PE/EtOAc ethergradient @ 30 mL/min) to give intermediate **31A** (42 mg, 98.1 umol, 8.0% yield) as a white solid.

3-(2,4-dichloroquinazolin-7-yl)-*N*-[4-(trifluoromethyl)phenyl]pyrazin-2-amine

[00289] To a solution of intermediate **31A** (41.90 mg, 0.10 mmol, 1 *eq*) was added $POCl_3$ (825.0 mg, 5.38 mmol, 0.50 mL, 51 *eq*) and N,N-diethylaniline (37.5 mg, 0.25 mmol, 40.2 uL, 2.4 *eq*). The reaction mixture was stirred at 100 °C for 4 hrs. After cooling, the reaction mixture was evaporated, and the mixture was diluted with H_2O and $CHCl_3$. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 3), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by flash chromatography on silica gel (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~20% PE/EtOAc ethergradient @ 25 mL/min) to afford **Compound 31** (7.37 mg, 15.1% yield) as a yellow solid. LC-MS (ESI): RT = 1.044 min, mass calcd for $C_{19}H_{10}Cl_2F_3N_5$ 436.22 m/z found 436.0 [M]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 - 8.44 (m, 2H), 8.30 (q, *J* = 2.6 Hz, 2H), 8.15 (dd, *J* = 1.6, 8.7 Hz, 1H), 7.61 (q, *J* = 9.0 Hz, 4H), 6.93 (s, 1H).

Example 32: 2-Methyl-8-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine 1,1-dioxide (Compound 32)



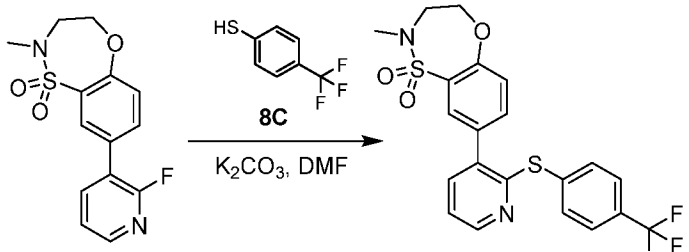
2-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

[00290] A mixture of 8-bromo-2-methyl-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide (**34E**, 100 mg, 0.34 mmol, 1 *eq*), **6C** (130.4 mg, 0.51 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (25.1 mg, 34.2 umol, 0.1 *eq*), KOAc (50.4 mg, 0.51 mmol, 1.5 *eq*) in dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 2 hrs under N_2 atmosphere. The reaction mixture containing the product intermedidate **32A** was used for the next step.

2-methyl-8-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

[00291] A mixture of intermedidate **32A** (1 *eq*), 2-chloro-3-((4-(trifluoromethyl)phenyl)thio)pyrazine (**32B**, 95.9 mg, 0.33 mmol, 1 *eq*), $Pd(dppf)Cl_2$ (24.2 mg, 33.0 umol, 0.1 *eq*), K_2CO_3 (68.4 mg, 0.50 mmol, 1.5 *eq*) in H_2O (1 mL) and dioxane (1 mL) was degassed and purged with N_2 for 3 times, and then the reaction mixture was stirred at 100 °C for 3 hr under N_2 atmosphere. The reaction mixture was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 45%-75%, 8.5min) to afford **Compound 32** (8.6 mg, 5.4% yield) as a yellow solid. LC-MS (ESI): RT = 0.956 min, mass calcd for $C_{20}H_{16}F_3N_3O_3S_2$ 467.06, m/z found 468.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 2.5 Hz, 1H), 8.45 (d, *J* = 2.5 Hz, 1H), 8.09 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.80 - 7.75 (m, 1H), 7.73 - 7.68 (m, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 4.32 - 4.23 (m, 2H), 3.77 - 3.68 (m, 2H), 2.75 (s, 3H).

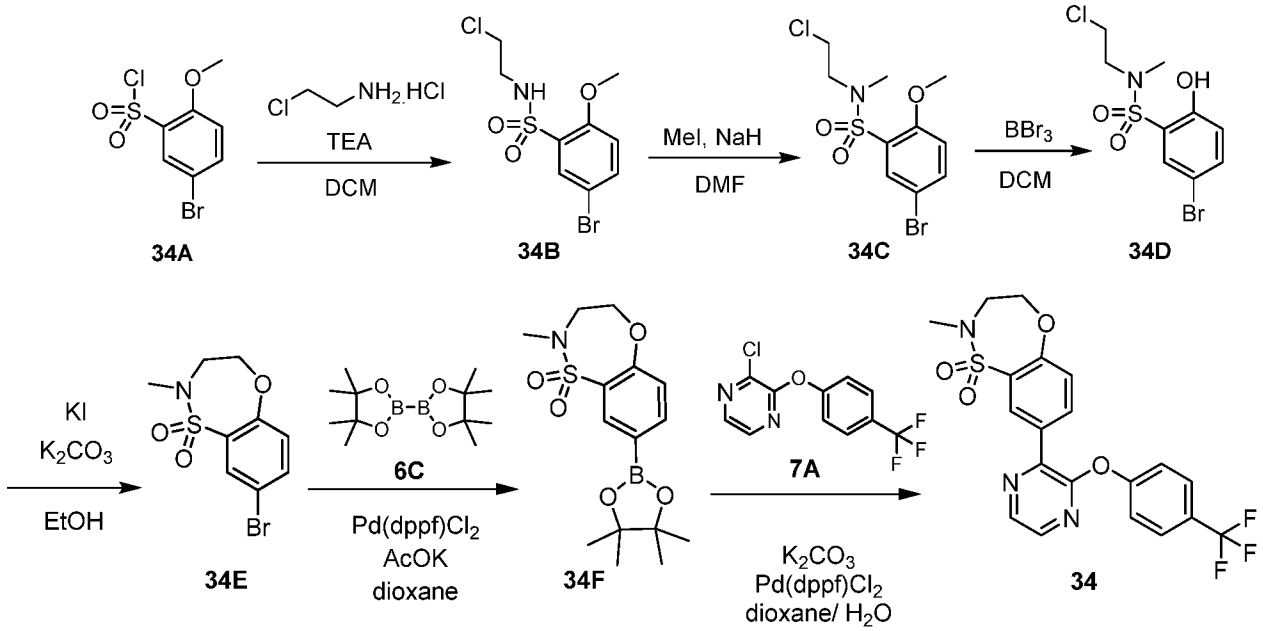
Example 33: 2-Methyl-8-(2-((4-(trifluoromethyl)phenyl)thio)pyridin-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine 1,1-dioxide (Compound 33)



[00292] To a solution of 8-(2-fluoropyridin-3-yl)-2-methyl-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide (**35A**, 60 mg, 0.19 mmol, 1 *eq*) in DMF (2 mL) were added K_2CO_3 (53.8 mg, 0.39 mmol, 2 *eq*) and 4-(trifluoromethyl)benzenethiol (**8C**, 38.1 mg, 0.21 mmol, 1.1 *eq*). The reaction mixture was stirred at 100 °C for 2 hrs. The reaction mixture was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water (0.04%NH_3H_2O+10mM NH4HCO3)-ACN]; B%: 46%-76%, 9.5min) to afford **Compound 33** (12.6 mg, 13.9% yield) as a white solid. LC-MS (ESI): RT = 0.888 min, mass calcd for $C_{21}H_{17}F_3N_2O_3S_2$ 466.06, m/z found

467.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.42 (dd, J = 1.5, 4.6 Hz, 1H), 7.81 - 7.69 (m, 5H), 7.60 (d, J = 8.3 Hz, 2H), 7.42 - 7.35 (m, 2H), 4.29 - 4.20 (m, 2H), 3.72 (d, J = 3.8 Hz, 2H), 2.73 (s, 3H).

Example 34: 2-Methyl-8-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine 1,1-dioxide (Compound 34)



5-bromo-N-(2-chloroethyl)-2-methoxy-benzenesulfonamide

[00293] To a solution of 5-bromo-2-methoxybenzenesulfonyl chloride (**34A**, 9 g, 31.52 mmol, 1 *eq*) in DCM (120 mL) was added triethylamine (TEA, 9.57 g, 94.56 mmol, 13.2 mL, 3 *eq*) and 2-chloroethanamine (4.39 g, 37.82 mmol, 1.2 *eq*, HCl). The reaction mixture was stirred at 20 °C for 3 hrs. The reaction mixture was diluted with H_2O (50 mL) and the reaction mixture was acidified with HCl (2 M) to pH = 2. The aqueous phase was extracted with EtOAc (100 mL x 3). The combined organic phase was washed with brine (120 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **34B** (9.8 g, crude) as a white solid, which was used for next step without further purification.

5-bromo-N-(2-chloroethyl)-2-methoxy-N-methyl-benzenesulfonamide

[00294] To a solution of intermediate **34B** (4.2 g, 12.78 mmol, 1 *eq*) in DMF (50 mL) was added NaH (766.8 mg, 19.17 mmol, 60% purity, 1.5 *eq*) at 0 °C under N_2. After addition, the reaction mixture was stirred at 0°C for 0.5 hr, and then iodomethane (2.72 g, 19.17 mmol, 1.19 mL, 1.5 *eq*) was added dropwise at 20 °C. The resulting mixture was stirred at 20 °C for 2.5 hrs. The reaction mixture was quenched by addition NH_4Cl (80 mL) at 0 °C, and then diluted with EtOAc

(30 mL). The aqueous phase was extracted with EtOAc (80 mL x 3). The combined organic phase was washed with brine (80 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by flash chromatography on silica gel (40 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~20%) to give intermediate **34C** (3.1 g, 9.05 mmol, 70.79% yield) as a white solid.

5-bromo-N-(2-chloroethyl)-2-hydroxy-N-methyl-benzenesulfonamide

[00295] To a solution of intermediate **34C** (2.9 g, 8.46 mmol, 1 *eq*) in DCM (30 mL) was added dropwise BBr_3 (2.54 g, 10.16 mmol, 0.98 mL, 1.2 *eq*) in DCM (3 mL) at 0 °C under N_2. After addition the mixture was stirred at 0 °C for 1 hr. The reaction mixture was quenched by addition H_2O (50 mL) at 0 °C, and then diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **34D** (2.7 g, crude) as a white solid, which was used for next step without further purification.

8-bromo-2-methyl-3,4-dihydro-5,1λ⁶,2-benzoxathiazepine 1,1-dioxide

[00296] To a solution of intermediate **34D** (2.5 g, 7.61 mmol, 1 *eq*) in EtOH (30 mL) was added KI (252.6 mg, 1.52 mmol, 0.2 *eq*) and K_2CO_3 (2.63 g, 19.02 mmol, 2.5 *eq*). The reaction mixture was stirred at 80 °C for 16 hrs. The reaction mixture was poured into H_2O (50 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (40 mL x 3). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give crude intermediate **34E** (2.06 g, crude) as a white solid, which was used for next step without further purification.

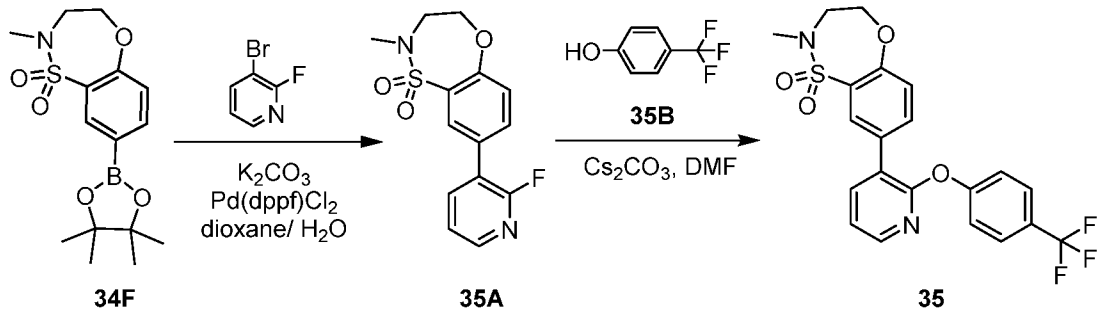
2-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

[00297] A mixture of intermediate **34E** (200 mg, 0.68 mmol, 1 *eq*), **6C** (260.8 mg, 1.03 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (50.1 mg, 68.5 umol, 0.1 *eq*), KOAc (100.8 mg, 1.03 mmol, 1.5 *eq*) in dioxane (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80 °C for 2 hrs under N_2 atmosphere. The reaction mixture containing product intermediate **34F** was used for the next step.

2-methyl-8-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

[00298] A mixture of intermediate **34F** (0.12 M, 5 mL, 1 *eq*), **7A** (164.8 mg, 0.6 mmol, 1 *eq*), Pd(dppf)Cl_2 (43.9 mg, 60.0 umol, 0.1 *eq*), K_2CO_3 (124.4 mg, 0.9 mmol, 1.5 *eq*) in dioxane (3 mL) and H_2O (1 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90 °C for 3 hrs under N_2 atmosphere. The residue was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by =rep-HPLC (column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 50%-80%, 7.8min) to afford **Compound 34** (52.8 mg, 19.3% yield) as a white solid. LC-MS (ESI): RT = 0.885 min, mass calcd for $C_{20}H_{16}F_3N_3O_4S$ 451.08, m/z found 452.0 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.57 (d, *J* = 2.5 Hz, 1H), 8.50 (d, *J* = 2.3 Hz, 1H), 8.40 (dd, *J* = 2.3, 8.5 Hz, 1H), 8.23 (d, *J* = 2.5 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 4.33 - 4.23 (m, 2H), 3.77 - 3.67 (m, 2H), 2.75 (s, 3H).

Example 35: 2-Methyl-8-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine 1,1-dioxide (Compound 35)



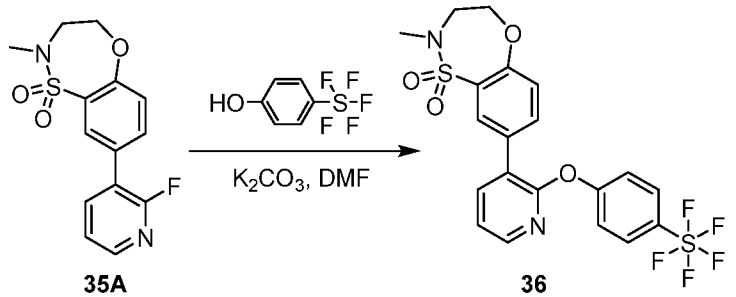
2-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide

[00299] A mixture of intermediate **34F** (0.27 M, 10 mL, 1 *eq*), 3-bromo-2-fluoropyridine (522.7 mg, 2.97 mmol, 1.1 *eq*), Pd(dppf)Cl_2 (197.6 mg, 0.27 mmol, 0.1 *eq*), K_2CO_3 (559.8 mg, 4.05 mmol, 1.5 *eq*) in H_2O (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 3 hr under N_2 atmosphere. The residue was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3).The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue. The residue was purified by flash chromatography on silica gel (20 g SepaFlash® Silica Flash Column, EtOAc/PE: 0~50%) to give intermediate **35A** (218 mg, 0.61 mmol, 22.5% yield) as a yellow solid.

2-methyl-8-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]-3,4-dihydro-5,1λ^6,2-benzoxathiazepine 1,1-dioxide

[00300] To a solution of intermediate **35A** (60 mg, 0.19 mmol, 1 *eq*) in DMF (2 mL) were added Cs_2CO_3 (95.1 mg, 0.29 mmol, 1.5 *eq*) and 4-(trifluoromethyl)phenol (**35B**, 37.9 mg, 0.23 mmol, 1.2 *eq*). The reaction mixture was stirred at 100 °C for 16 hrs. The reaction mixture was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by prep-HPLC (column: Waters Xbridge 150 x 25mm x 5um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 45%-75%, 9.5min) to afford **Compound 35** (12.7 mg, 14.49% yield) as a white solid. LC-MS (ESI): RT = 0.881 min, mass calcd for $C_{21}H_{17}F_3N_2O_4S$ 450.09, m/z found 450.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (d, *J* = 3.3 Hz, 1H), 8.06 (d, *J* = 7.3 Hz, 1H), 8.01 - 7.92 (m, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.41 - 7.31 (m, 4H), 4.24 (s, 2H), 3.70 (d, *J* = 3.8 Hz, 2H), 2.71 (s, 3H).

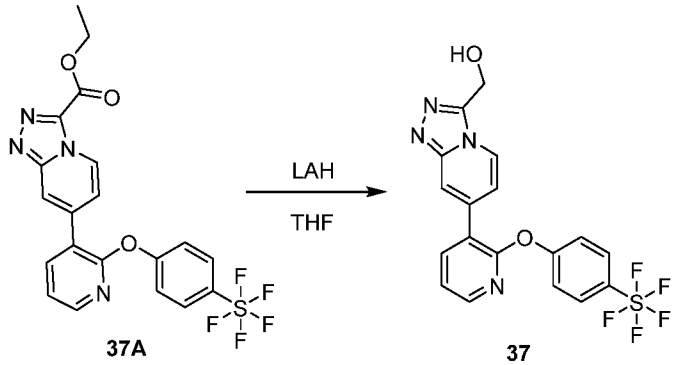
Example 36: 2-Methyl-8-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2*H*-benzo[*b*][1,4,5]oxathiazepine 1,1-dioxide (Compound 36)



[00301] To a solution of intermediate **35A** (60 mg, 0.19 umol, 1 *eq*) in DMF (1 mL) were added K_2CO_3 (40.3 mg, 0.29 mmol, 1.5 *eq*) and 4-(pentafluoro-λ6-sulfaneyl)phenol (51.4 mg, 0.23 mmol, 1.2 *eq*). The reaction mixture was stirred at 100 °C for 36 hrs. The reaction mixture was poured into H_2O (30 mL) and stirred for 5 min. The aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum to give residue, which was purified by Prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water (0.04%NH3H2O+10mM NH4HCO3)-ACN]; B%: 50%-80%, 7.8min) to afford **Compound 36** (23.9 mg, 24.2% yield) as a white solid. LC-MS (ESI): RT = 0.902 min, mass calcd for $C_{20}H_{17}F_5N_2O_4S_2$ 508.05, m/z found 508.9 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.20 (dd, *J* = 1.8, 4.8 Hz, 1H), 8.07 - 7.98 (m, 2H),

7.89 - 7.81 (m, 3H), 7.37 - 7.29 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 4.26 - 4.20 (m, 2H), 3.80 - 3.74 (m, 2H), 2.77 (s, 3H).

Example 37: (7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)methanol (Compound 37)



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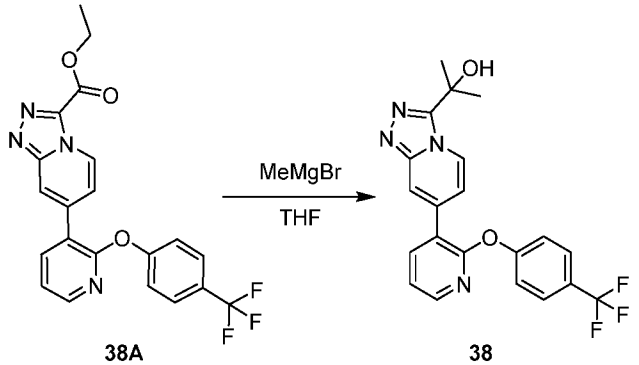
[00302] $LiAlH_4$ (89.5 mg, 4.11 mmol, 5 *eq*) was added at the mixture of ethyl 7-[2-[4-(pentafluoro-λ^6-sulfanyl)phenoxy]-3-pyridyl]-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (**37A**, 400 mg, 0.82m mol, 1 *eq*) in THF (4 mL) at 0°C. Then the reaction mixture was stirred at 25°C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with EtOAc (20 mL x 3). The combined organic phase was washed with brine (10mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 x 25mm x 5um; mobile phase: [water (0.05%NH_3H_2O)-ACN]; B%: 37%-67%, 9.5min) to afford **Compound 37** (3.2 mg, 3.2% yield) as colorless oil. LC-MS (ESI): RT = 0.829 min, mass calcd for $C_{18}H_{13}F_5N_4O_2S$ 444.38 m/z found 445.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.02 (dd, *J* = 0.9, 7.3 Hz, 1H), 8.43 (s, 1H), 8.34 (dd, *J* = 1.8, 4.9 Hz, 1H), 8.27 (dd, *J* = 1.8, 7.6 Hz, 1H), 8.02 (dd, *J* = 1.4, 7.2 Hz, 1H), 7.95 - 7.90 (m, 2H), 7.44 (dd, *J* = 4.9, 7.6 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 5.25 (s, 2H).

Example 38: 2-(7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-*a*]pyridin-3-yl)propan-2-ol (Compound 38)



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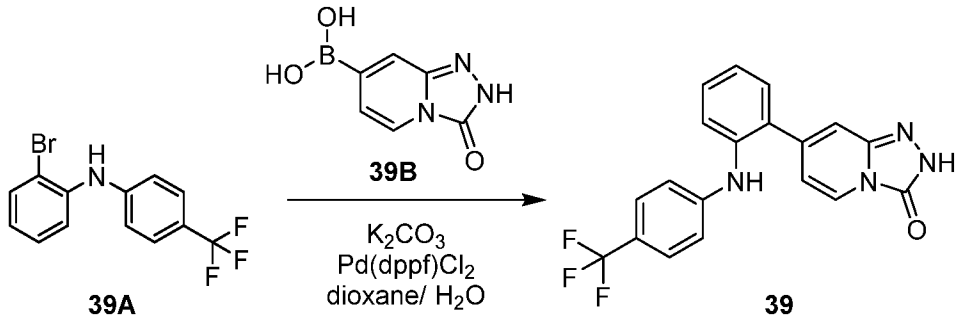
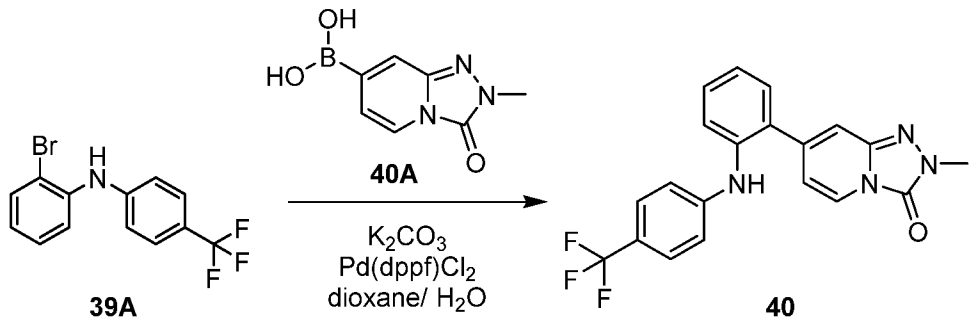
[00303] MeMgBr (3M, 0.19 mL, 5 *eq*) was added at the mixture of ethyl 7-[2-[4-(trifluoromethyl)phenoxy]-3-pyridyl]-[1,2,4]triazolo[4,3-a]pyridine-3-carboxylate (**38A**, 50 mg, 0.11 mmol, 1 *eq*) in THF (1 mL) dropwise at 0 °C. Then the reaction mixture was stirred at 25 °C for 1 hr. The reaction mixture was diluted with H_2O (10 mL) and the mixture was extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine (10 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: 3_Phenomenex Luna C18 75 x 30mm x 3um; mobile phase: [water (0.05%HCl)-ACN]; B%: 23%-53%,8.5min) to afford **Compound 38** (6.78 mg, 14.0% yield) as a white solid. LC-MS (ESI): RT = 0.768 min, mass calcd for $C_{21}H_{17}F_3N_4O_2$ 414.38 m/z found 415.0$[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 9.03 (d, J = 7.3 Hz, 1H), 8.32 - 8.26 (m, 2H), 8.24 (dd, J = 1.8, 7.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.69 (dd, J = 1.5, 7.3 Hz, 1H), 7.72 - 7.65 (m, 1H), 7.47 (d, J = 8.5 Hz, 2H), 7.42 (dd, J = 4.9, 7.4 Hz, 1H), 1.73 (s, 6H).

Example 39: 7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (Compound 39)



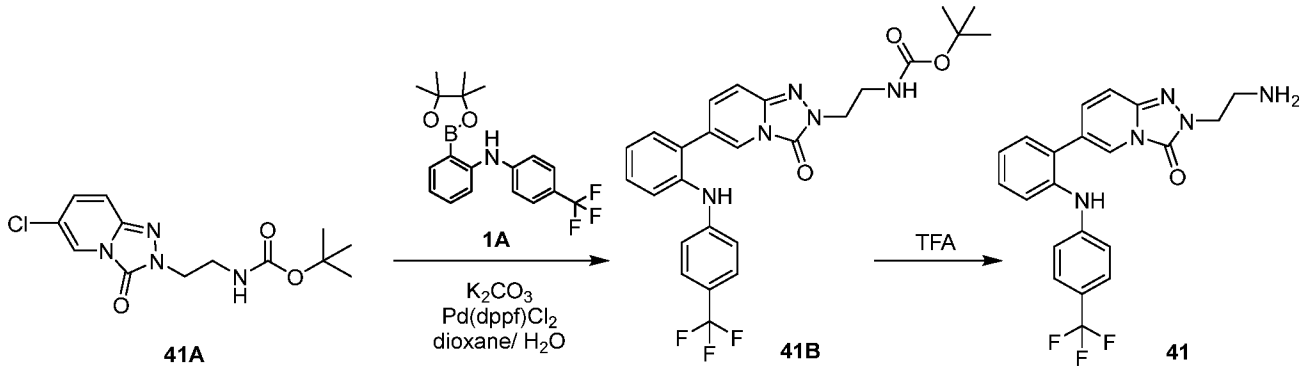
[00304] 2-Bromo-N-(4-(trifluoromethyl)phenyl)aniline (**39A**, 1 eq) and [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-7-boronic acid (**39B**, 1.2 eq.) were suspended in K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added Pd(dppf)Cl2 (0.1 eq.) and the mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 39** (84%). Calcd.: 370.1, m/z found: 371.1 ($[M+H]^+$).

Example 40: 2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (Compound 40)



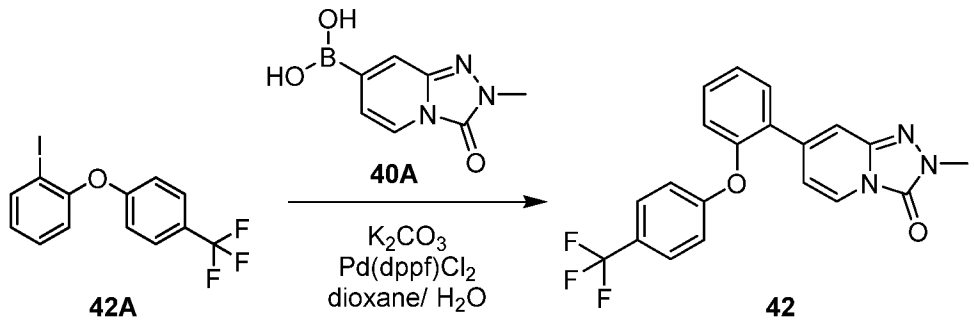
[00305] **Compound 40** was prepared by employing the procedure for **Compound 39** using (2-methyl-3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyridin-7-yl)boronic acid (**40A**) in lieu of [1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-7-boronic acid (**39B**). Calcd.: 384.1, m/z found: 385.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 3.49 - 3.54 (m, 3 H) 6.54 (dd, *J*=7.34, 1.47 Hz, 1 H) 6.90 (d, *J*=8.53 Hz, 2 H) 7.20 (t, *J*=1.15 Hz, 1 H) 7.24 (td, *J*=7.40, 1.33 Hz, 1 H) 7.38 - 7.47 (m, 5 H) 7.79 (dd, *J*=7.29, 0.96 Hz, 1 H) 8.20 (s, 1 H).

Example 41: 2-(2-Aminoethyl)-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one (Compound 41)



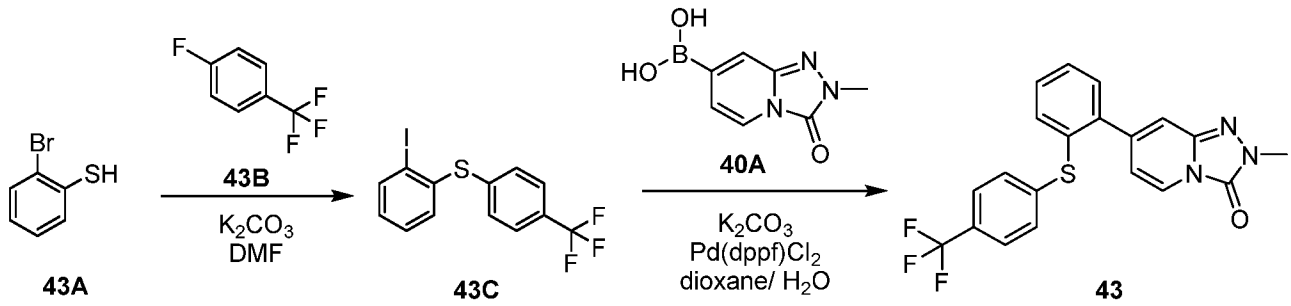
[00306] **Compound 41** was prepared by employing the procedure for **Compound 39** using *tert*-butyl (2-(6-chloro-3-oxo-[1,2,4]triazolo[4,3-a]pyridin-2(3*H*)-yl)ethyl)carbamate (**41A**) and compound **1A** in lieu of **39A** and **39B**, respectively, followed by treatment with trifluoracetic acid to remove the Boc protecting group. Calcd.: 413.1, m/z found: 414.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 3.18 - 3.31 (m, 3 H) 4.12 - 4.19 (m, 6 H) 6.63 (dd, *J*=7.34, 1.47 Hz, 1 H) 6.88 (d, *J*=8.44 Hz, 2 H) 7.25 - 7.34 (m, 2 H) 7.39 - 7.52 (m, 5 H) 7.82 - 7.94 (m, 5 H) 8.26 (s, 1 H).

Example 42: 2-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one (Compound 42)



[00307] 1-Iodo-2-(4-(trifluoromethyl)phenoxy)benzene (**42A**, 36 mg, 0.1 mmol, 1 eq) and 2-methyl-)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one-7-boronic acid (**40A**, 24 mg, 0.12 mmol, 1.2 eq.) were suspended in 1:4 K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (7 mg, 0.1 eq.) and the reaction mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried with Na_2SO_4, concentrated, and purified by flash chromatography (DCM/EtOAc gradient) to afford **Compound 42** (34 mg, 87%). LC-MS Calcd.: 385.1 m/z found: 386.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 3.53 (s, 3 H) 6.76 (dd, *J*=7.34, 1.10 Hz, 1 H) 7.11 (d, *J*=8.80 Hz, 2 H) 7.20 (d, *J*=8.07 Hz, 1 H) 7.31 (s, 1 H) 7.42 (t, *J*=7.52 Hz, 1 H) 7.54 (t, *J*=7.79 Hz, 1 H) 7.65 - 7.72 (m, 3 H) 7.84 (d, *J*=7.34 Hz, 1 H).

Example 43: 2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one (Compound 43)



(2-Bromophenyl)(4-(trifluoromethyl)phenyl)sulfane

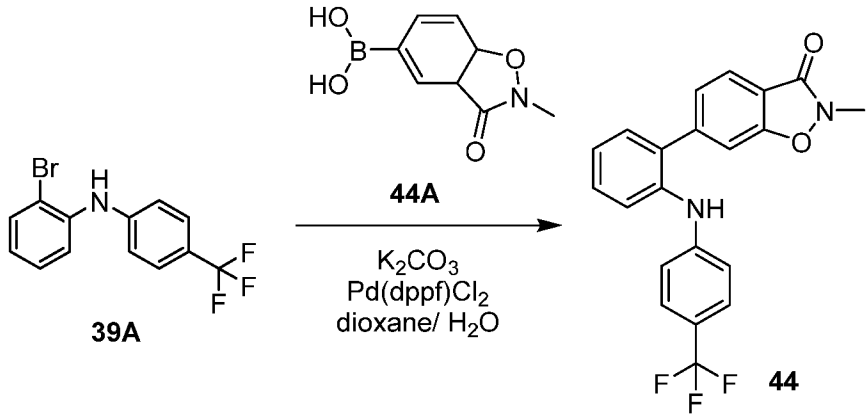
[00308] 2-Bromobenzenethiol (**43A**, 0.604 g, 1 eq.), 1-fluoro-4-(trifluoromethyl)benzene (**43B**, 0.64 g, 1.2 eq.), K_2CO_3 (1.31 g, 3 eq.), and DMF (5 mL) were heated to 85 °C for 18 hr. The reaction mixture was slowly added to rapidly stirring H_2O (30 mL), the resulting precipitate was

filtered, and washed several times with H_2O to give intermediate **43C** (720 mg, 70%). LC-MS Calcd.: 331.9 m/z found: 333 ($[M+H]^+$).

2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one

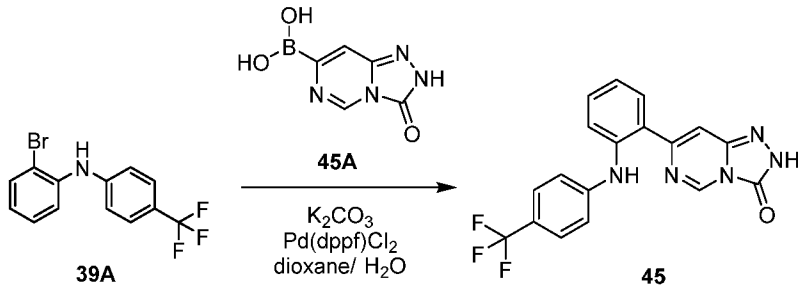
[00309] Intermediate **43C** (1 eq) and 1-methyl-[1,2,4]triazolo[4,3-a]pyridine-3(2H)-one-7-boronic acid (**40A**, 1.2 eq.) were suspended in K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq.) and the mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to rt, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried with Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 43**. LC-MS Calcd.: 401.1 m/z found: 402.0 ($[M+H]^+$).

Example 44: 2-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)benzo[d]isoxazol-3(2*H*)-one (Compound 44)



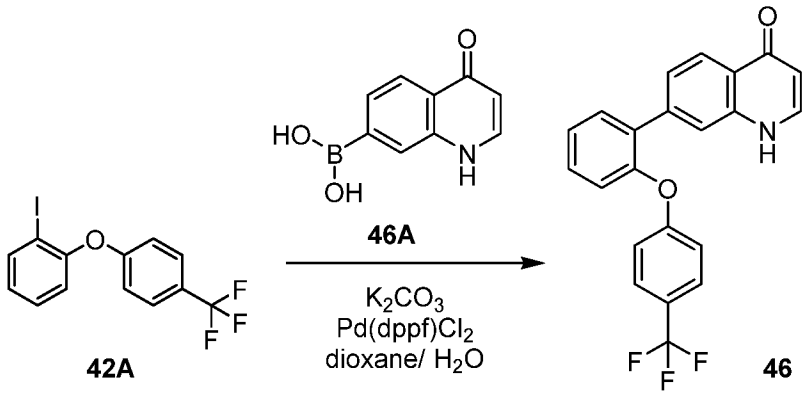
[00310] **Compound 44** was prepared by employing the procedure for **Compound 39** using (2-methyl-3-oxo-2,3,3a,7a-tetrahydrobenzo[d]isoxazol-5-yl)boronic acid (**44A**) in lieu of **39B**. LCMS Calcd.: 384.1 m/z found: 385.0 ($[M+H]^+$). 1H NMR (600 MHz, DMSO-d6) δ ppm 3.57 - 3.62 (m, 3 H) 6.86 (d, *J*=8.44 Hz, 2 H) 7.25 - 7.32 (m, 1 H) 7.34 - 7.50 (m, 8 H) 7.74 - 7.86 (m, 1 H) 8.15 (s, 1 H).

Example 45: 7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-*c*]pyrimidin-3(2*H*)-one (Compound 45)



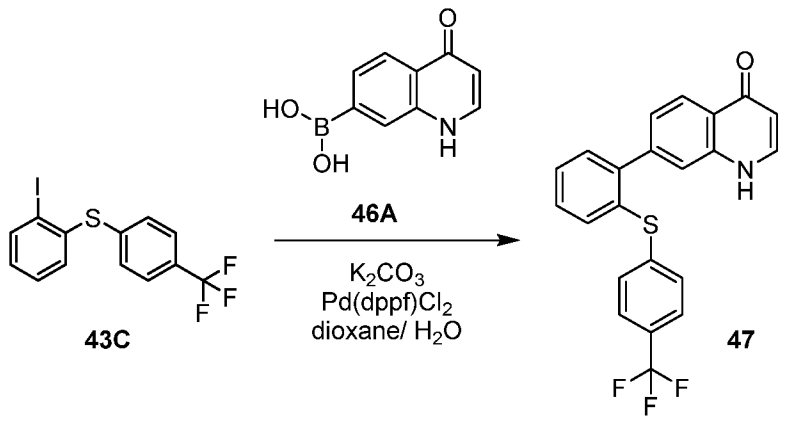
[00311] **Compound 45** was prepared by employing the procedure for **Compound 39** using (3-oxo-2,3-dihydro-[1,2,4]triazolo[4,3-c]pyrimidin-7-yl)boronic acid (**45A**) in lieu of **39B**. LC-MS Calcd.: 384.1 m/z found: 385.0 ([M+H]$^+$). 1H NMR (600 MHz, DMSO-d6) δ ppm 3.57 - 3.62 (m, 3 H) 6.86 (d, *J*=8.44 Hz, 2 H) 7.25 - 7.32 (m, 1 H) 7.34 - 7.50 (m, 8 H) 7.74 - 7.86 (m, 1 H) 8.15 (s, 1 H).

Example 46: 7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one (Compound 46)



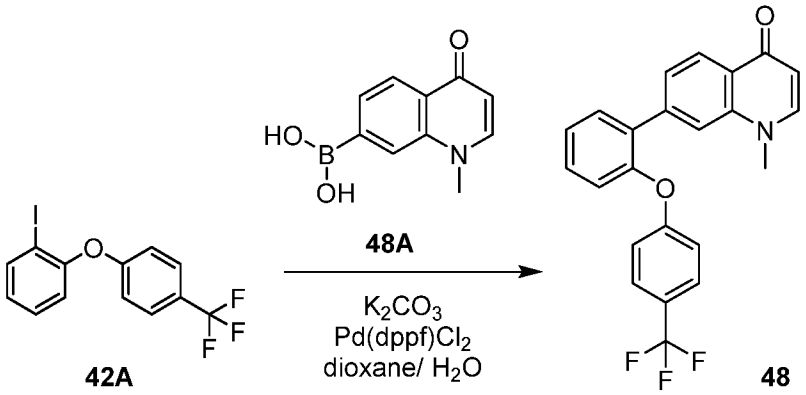
[00312] **Compound 46** was prepared by employing the procedure for **Compound 42** using (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**) in lieu of **40A**. LC-MS mass calcd. $C_{22}H_{14}F_3NO_2$, 381. m/z found, 382 [M+H]$^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 6.02 (d, *J*=7.70 Hz, 1 H) 6.66 (s, 1 H) 6.88 (s, 2 H) 7.05 (d, *J*=8.44 Hz, 2 H) 7.25 (dd, *J*=8.07, 1.10 Hz, 1 H) 7.42 - 7.46 (m, 2 H) 7.54 (t, *J*=7.85 Hz, 1 H) 7.64 - 7.68 (m, 4 H) 7.90 (d, *J*=7.34 Hz, 1 H) 8.06 (d, *J*=8.44 Hz, 1 H) 11.77 (br s, 1 H).

Example 47: 7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one (Compound 47)



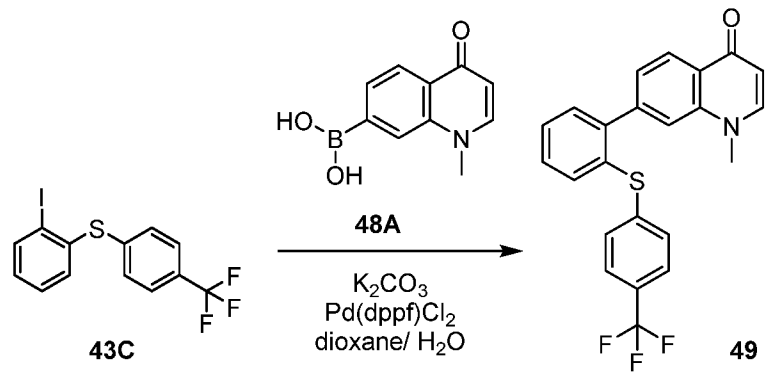
[00313] **Compound 47** was prepared by employing the procedure for **Compound 43** using (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**) in lieu of **42A**. LC-MS mass calcd., $C_{22}H_{14}F_3NOS$, 397. m/z found, 398 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 6.24 (d, *J*=7.34 Hz, 1 H) 7.23 (d, *J*=8.44 Hz, 2 H) 7.37 (dd, *J*=8.07, 1.47 Hz, 1 H) 7.52 - 7.65 (m, 9 H) 8.07 (br d, *J*=6.97 Hz, 1 H) 8.10 (d, *J*=8.07 Hz, 1 H) 12.27 (br s, 1 H).

Example 48: 1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one (Compound 48)



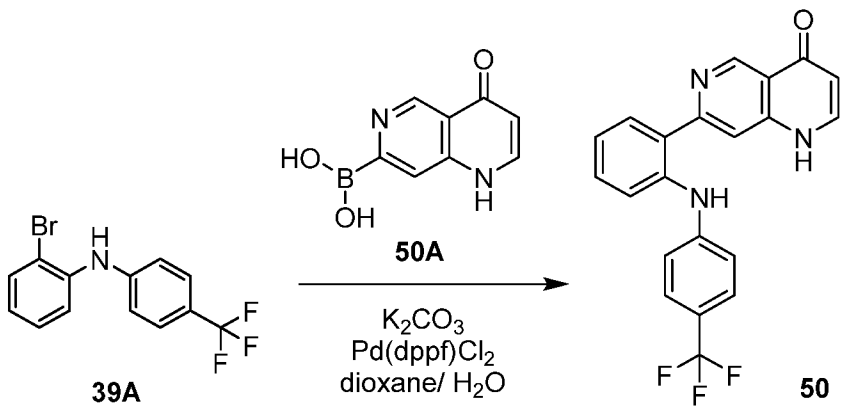
[00314] **Compound 48** was prepared by employing the procedure for **Compound 42** using (1-methyl-4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**48A**) in lieu of **40A**. LC-MS Calcd.: 396.4 ([M+H]+), m/z found: 396.1. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 3.73 (s, 3 H) 6.03 (d, *J*=7.34 Hz, 1 H) 7.08 (d, *J*=8.80 Hz, 2 H) 7.27 (dd, *J*=8.25, 0.92 Hz, 1 H) 7.47 (td, *J*=7.52, 1.10 Hz, 1 H) 7.53 (dd, *J*=8.07, 1.47 Hz, 1 H) 7.56 (td, *J*=7.79, 1.65 Hz, 1 H) 7.65 - 7.69 (m, 3 H) 7.74 (dd, *J*=7.52, 1.65 Hz, 1 H) 7.95 (d, *J*=7.70 Hz, 1 H) 8.14 (d, *J*=8.44 Hz, 1 H).

Example 49: 1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one (Compound 49)



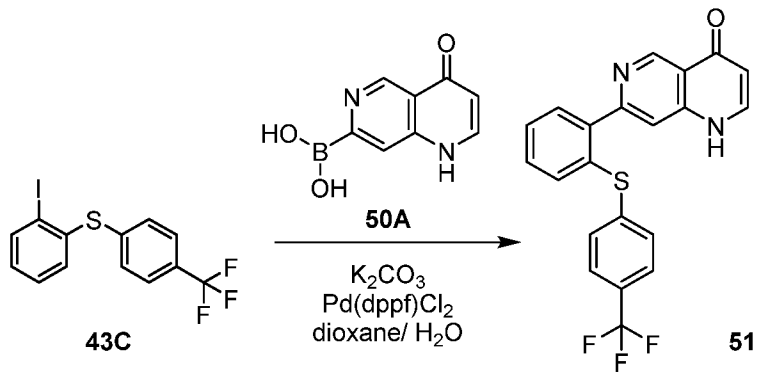
[00315] **Compound 49** was prepared by employing the procedure for **Compound 43** using (1-methyl-4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**48A**) in lieu of **40A**. LC-MS Calcd.: 412 ($[M+H]^+$), m/z found: 412. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.65 (s, 3 H) 6.04 (d, J=7.34 Hz, 1 H) 7.22 (d, J=8.44 Hz, 2 H) 7.38 (dd, J=8.44, 1.47 Hz, 1 H) 7.47 (d, J=1.47 Hz, 1 H) 7.55 - 7.66 (m, 6 H) 7.95 (d, J=7.70 Hz, 1 H) 8.14 (d, J=8.44 Hz, 1 H).

Example 50: 7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-1,6-naphthyridin-4(1*H*)-one (Compound 50)



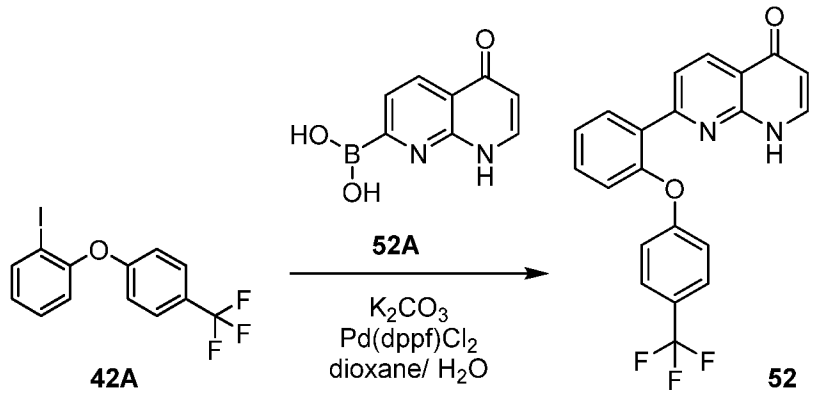
[00316] **Compound 50** was prepared by employing the procedure for **Compound 39** using (4-oxo-1,4-dihydro-1,6-naphthyridin-7-yl)boronic acid (**50A**) in lieu of **39B**. LC-MS Calcd.: 381.1 m/z found: 382.0 ($[M+H]^+$). 1H NMR (600 MHz, DMSO-d6) δ ppm 6.16 (d, *J*=7.70 Hz, 1 H) 7.14 (d, *J*=8.80 Hz, 2 H) 7.22 (t, *J*=7.55 Hz, 1 H) 7.44 - 7.52 (m, 4 H) 7.72 (s, 1 H) 7.74 (dd, *J*=7.70, 1.47 Hz, 1 H) 7.98 (d, *J*=7.34 Hz, 1 H) 9.31 (s, 1 H) 9.49 (s, 1 H) 11.95 (br s, 1 H).

Example 51: 7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-1,6-naphthyridin-4(1*H*)-one (Compound 51)



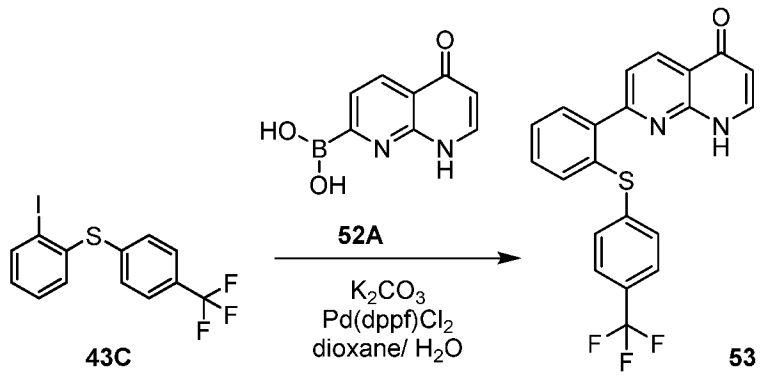
[00317] **Compound 51** was prepared by employing the procedure for **Compound 43** using ((4-oxo-1,4-dihydro-1,6-naphthyridin-7-yl)boronic acid (**50A**) in lieu of **40A**. LC-MS Calcd.: 398.1 m/z found: 399.0 ($[M+H]^+$).

Example 52: 7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one (Compound 52)



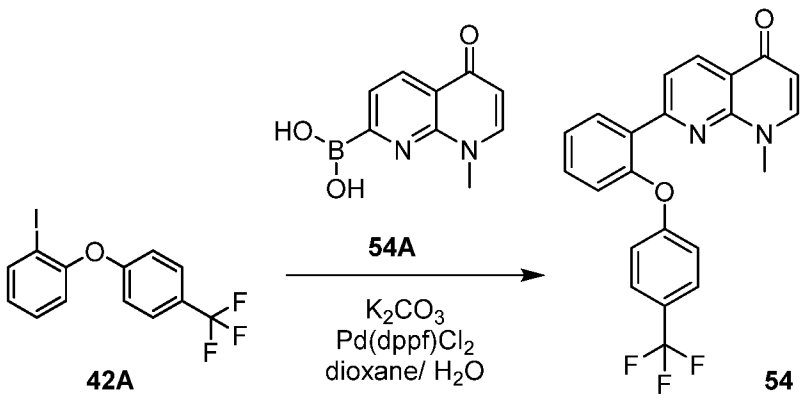
[00318] **Compound 52** was prepared by employing the procedure for **Compound 42** using (5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)boronic acid (**52A**) in lieu of **40A**. LC-MS Calcd.: 382.1 m/z found: 383.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 6.12 (d, J=7.34 Hz, 1 H) 7.11 (m, J=8.80 Hz, 2 H) 7.25 (d, J=8.41 Hz, 1 H) 7.41 - 7.53 (m, 1 H) 7.61 (td, J=7.79, 1.65 Hz, 1 H) 7.68 (m, J=8.80 Hz, 2 H) 7.76 (d, J=8.07 Hz, 1 H) 7.96 (t, J=6.44 Hz, 2 H) 8.42 (d, J=8.44 Hz, 1 H) 12.29 (br s, 1 H).

Example 53: 7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one (Compound 53)



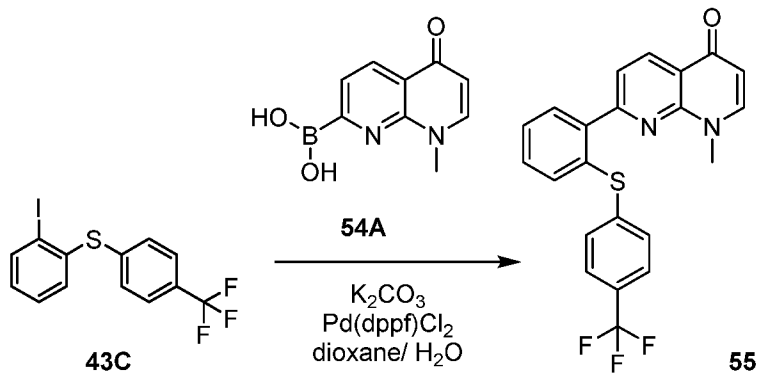
[00319] **Compound 53** was prepared by employing the procedure for **Compound 43** using (5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)boronic acid (**52A**) in lieu of **40A**. LC-MS Calcd.: 399 ([M+H]+), m/z found: 399. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.12 (d, J=7.70 Hz, 1 H) 6.88 (s, 1 H) 7.28 - 7.43 (m, 2 H) 7.46 - 7.64 (m, 5 H) 7.65 - 7.76 (m, 1 H) 7.94 (br d, J=5.13 Hz, 1 H) 8.47 (d, J=8.44 Hz, 1 H) 12.21 (br s, 1 H).

Example 54: 1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one (Compound 54)



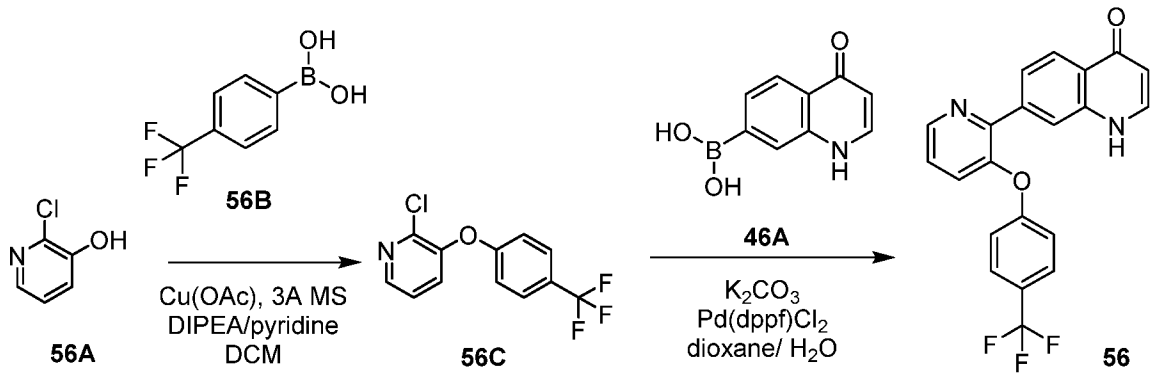
[00320] **Compound 54** was prepared by employing the procedure for **Compound 42** using (8-methyl-5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)boronic acid (**54A**) in lieu of **40A**. LC-MS Calcd.: 396.1 m/z found: 397.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.62 - 3.65 (m, 3 H) 6.14 (m, J=7.70 Hz, 1 H) 7.14 (d, J=8.44 Hz, 2 H) 7.28 (d, J=7.94 Hz, 1 H) 7.50 (t, J=7.48 Hz, 1 H) 7.62 - 7.73 (m, 3 H) 7.84 (d, J=8.07 Hz, 1 H) 8.04 (dd, J=7.70, 1.83 Hz, 1 H) 8.13 (m, J=7.70 Hz, 1 H) 8.50 (d, J=8.44 Hz, 1 H).

Example 55: 1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one (Compound 55)



[00321] **Compound 55** was prepared by employing the procedure for **Compound 43** (8-methyl-5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)boronic acid (**54A**) in lieu of **40A**. LC-MS Calcd.: 413 ([M+H]+), m/z found: 413. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.76 (s, 3 H) 6.15 (d, J=8.07 Hz, 1 H) 7.35 - 7.43 (m, 2 H) 7.44 - 7.51 (m, 1 H) 7.53 - 7.67 (m, 4 H) 7.73 (d, J=8.07 Hz, 1 H) 7.80 (dd, J=7.34, 1.83 Hz, 1 H) 8.14 (d, J=7.70 Hz, 1 H) 8.55 (d, J=8.07 Hz, 1 H).

Example 56: 7-(3-(4-(Trifluoromethyl)phenoxy)pyridin-2-yl)quinolin-4(1H)-one (Compound 56)



2-Chloro-3-(4-(trifluoromethyl)phenoxy)pyridine

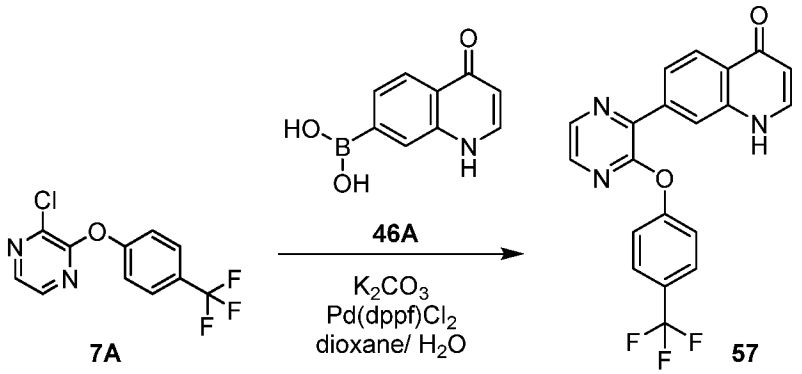
[00322] 2-Chloropyridin-3-ol (**56A**, 324 mg, 2.5 mmol, 1 eq.), (4-(trifluoromethyl)phenyl)boronic acid (**56B**, 570 mg, 3 mmol, 1.2 eq.), $Cu(OAc)_2$ (545 mg, 3 mmol, 1.2 eq.), 3 Å MS (200 mg), and DCM (12.5 mL, 0.2M) were stirred vigorously under dry air in a flask fitted with a $CaCl_2$ drying tube. DIEA (2.2 mL, 12.5 mmol, 5 eq.) and pyridine (1 mL, 12.5 mmol, 5 eq.) were slowly added, and the reaction mixture was stirred for 4 days at rt. The reaction mixture was diluted with sat. aq. NH_4Cl and filtered over celite and the filter cake was washed with DCM. The organic layer was washed with 1 N HCl, 1 N NaOH, H_2O, and brine. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column

chromatography eluting with DCM/EtOAc (0 to 100% gradient) to give intermediate **56C** (56 mg, 8%). %). LC-MS Calcd.: 274 ([M+H]$^+$), m/z found: 274.

7-(3-(4-(Trifluoromethyl)phenoxy)pyridin-2-yl)quinolin-4(1H)-one

[00323] Intermediate **56C** (27 mg, 0.1 mmol, 1 eq.) and (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**, 24 mg, 0.12 mmol, 1.2 eq.) were suspended in K_2CO_3 2M/dioxane (0.1/0.4 mL, 0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added Pd(dppf)Cl_2 (7 mg, 0.1 eq.) and the reaction mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography to afford **Compound 56** (11 mg, 29%). LC-MS Calcd.: 383 ([M+H]$^+$), m/z found: 383. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 6.34 (br d, J=6.97 Hz, 1 H) 7.21 (m, J=8.44 Hz, 2 H) 7.59 (dd, J=8.25, 4.58 Hz, 1 H) 7.74 (dd, J=8.25, 1.28 Hz, 3 H) 7.97 (d, J=8.56 Hz, 1 H) 8.18 (m, J=8.44 Hz, 2 H) 8.27 (s, 1 H) 8.68 (dd, J=4.58, 1.28 Hz, 1 H) 12.66 (br s, 1 H).

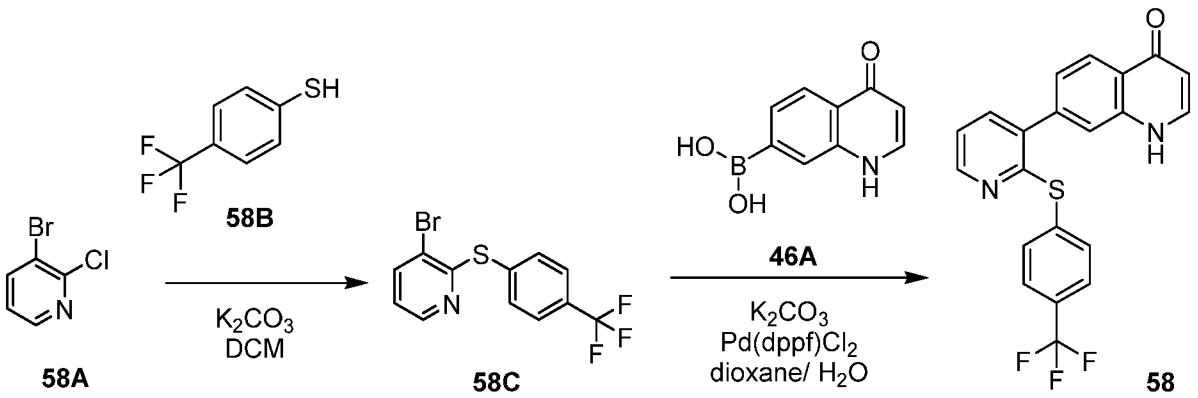
Example 57: 7-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one (Compound 57)



[00324] Intermediate **7A** (20 mg, 0.07 mmol, 1 eq.) and (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**, 23 mg, 0.087 mmol, 1.2 equiv.), were suspended in 1:4 K_2CO_3 2M/dioxane (0.1mL/0.4 mL, 0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added Pd(dppf)Cl_2 (7 mg, 0.1 eq.) and the reaction mixture was heated to 100 °C until LC-MS indicated the consumption of sm. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by flash column chromatograph to afford **Compound 57** (5 mg). LC-MS Calcd.: 384 ([M+H]$^+$), m/z found: 384. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.06 (dd, J=7.34, 1.19 Hz, 1 H) 6.85 (s, 1 H) 7.53 (d, J=8.44 Hz, 2 H) 7.84 (d, J=8.53 Hz, 2 H) 7.94 (dd,

J=7.38, 5.91 Hz, 1 H) 8.04 (d, J=1.65 Hz, 1 H) 8.19 (d, J=8.53 Hz, 1 H) 8.25 (d, J=2.48 Hz, 1 H) 8.36 (d, J=1.38 Hz, 1 H) 8.59 (d, J=2.57 Hz, 1 H) 11.94 (br d, J=5.59 Hz, 1 H).

Example 58: 7-(2-((4-(Trifluoromethyl)phenyl)thio)pyridin-3-yl)quinolin-4(1H)-one (Compound 58)



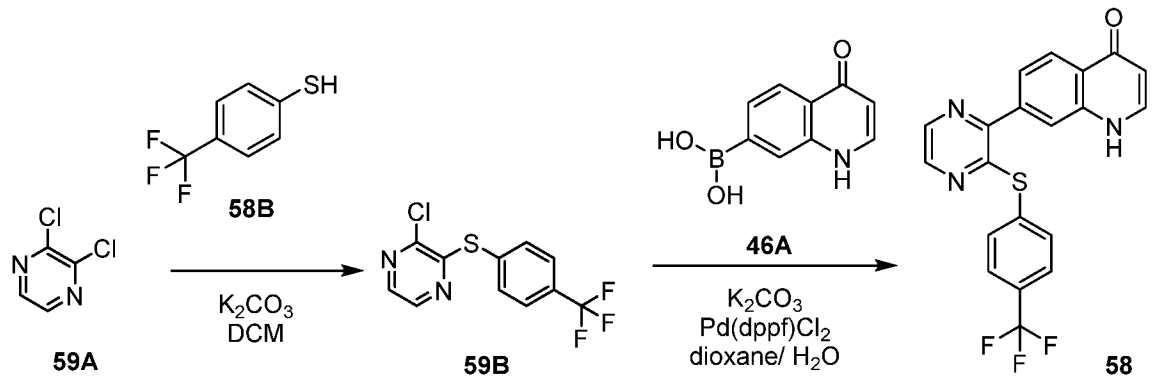
3-Bromo-2-((4-(trifluoromethyl)phenyl)thio)pyridine

[00325] 3-Bromo-2-chloropyridine (**58A**, 211 mg, 1.1 mmol, 1.1 eq.), 4-(trifluoromethyl)benzenethiol (**58B**, 0.135 mL, 1 mmol, 1 eq.), K_2CO_3 (276 mg, 2 mmol, 2 eq.), and DMF (3 mL, 0.33M) were stirred at 60 °C for 18 hr. The reaction mixture was added to rapidly stirring water, and the precipitate was filtered to give intermediate **58C** (104 mg, 31%). LC-MS Calcd.: 335 ($[M+H]^+$), m/z found: 335.

7-(2-((4-(Trifluoromethyl)phenyl)thio)pyridin-3-yl)quinolin-4(1H)-one

[00326] Intermediate **58C** 16 mg, 0.05 mmol, 1 eq.) and (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**, 14 mg, 0.05 mmol, 1 eq.) were suspended in 1:4 K_2CO_3 2M/dioxane (0.1 mL/ 0.4M mL 0.1M) and thoroughly purged with N_2 over 10 min. To this reaction was added $Pd(dppf)Cl_2$ (4 mg, 0.1 eq.) and the mixture was heated to 100 °C until LCMS indicated the consumption of sm. The reaction mixture was cooled to rt, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried with Na_2SO_4, concentrated, and purified by FCC to give the desired product. LCMS Calcd.: 399 ($[M+H]^+$), m/z found: 399.

Example 59: 7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one (Compound 59)



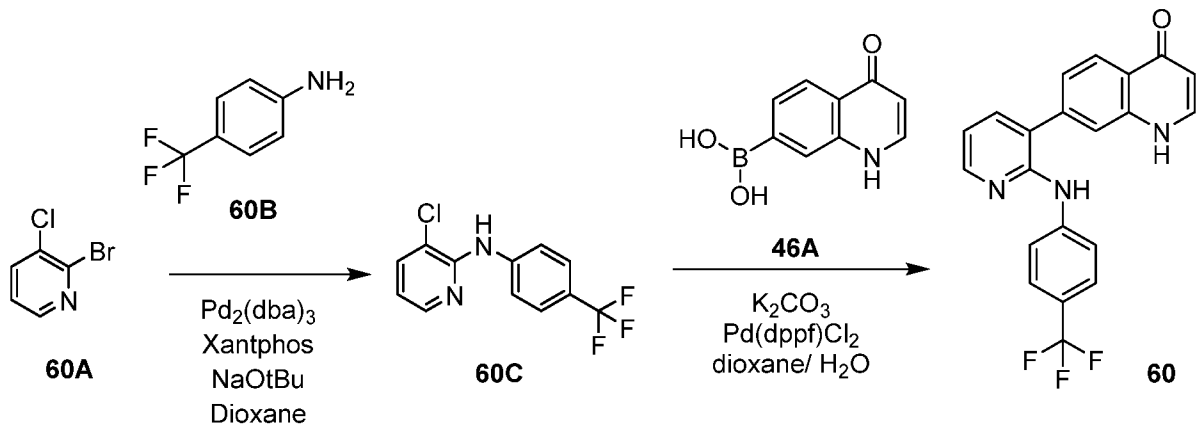
2-Chloro-3-((4-(trifluoromethyl)phenyl)thio)pyrazine

[00327] 2,3-Dichloropyrazine (**59A**, 1.56 g, 10.5 mmol, 1.05 eq.), 4-(trifluoromethyl)benzenethiol (**58B**, 1.35 mL, 10 mmol, 1 eq.), K_2CO_3 (2.8 g, 20 mmol, 2 eq.), and DMF (33 mL, 0.3M) were stirred at room temperature for 1 hr. The reaction mixture was added to rapidly stirring water, and the precipitate was filtered to give intermediate **59B** (2.35 g, 77%). LC-MS Calcd.: 291 ($[M+H]^+$), m/z found: 291.

7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one

[00328] Intermediate **59B** (2.35 g, 8 mmol, 1 eq.) and (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**, 1.81 g, 9.6 mmol, 1.2 equiv.) were suspended in 1:4 K_2CO_3 2M/dioxane (8 mL/32 mL, 0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (600 mg, 0.1 eq.) and the reaction mixture was heated to 100 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried overNa_2SO_4, concentrated, and purified by flash column chromatograph to afford **Compound 59**. LCMS Calcd.: 400 ($[M+H]^+$), m/z found: 400. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 6.11 (d, J=7.43 Hz, 1 H) 7.66 (d, J=8.20 Hz, 1 H) 7.72 (m, J=8.07 Hz, 2 H) 7.78 (m, J=8.07 Hz, 2 H) 7.93 (d, J=1.10 Hz, 1 H) 7.99 (t, J=6.56 Hz, 1 H) 8.23 (d, J=8.07 Hz, 1 H) 8.48 (d, J=2.57 Hz, 1 H) 8.60 (d, J=2.20 Hz, 1 H) 11.96 (br d, J=5.50 Hz, 1 H).

Example 60: 7-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4(1H)-one (Compound 60)



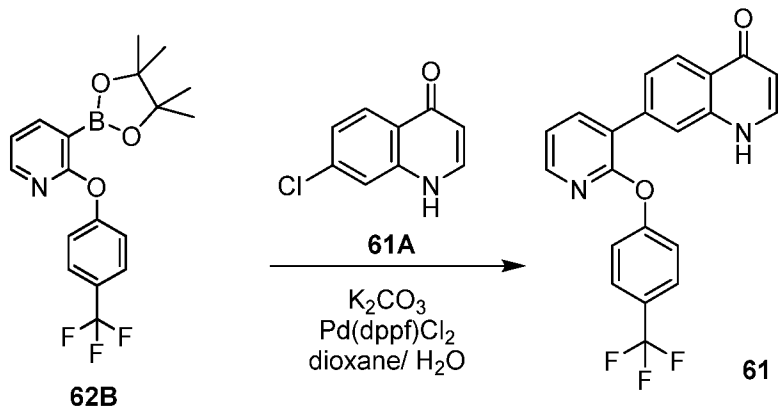
3-Chloro-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine

[00329] 2-Bromo-3-chloropyridine (**60A**, 1 eq.), 4-(trifluoromethyl)aniline (**60B**, 1 eq.), XantPhos (0.1 eq.), NaOtBu (2 eq.), and dioxane (0.2M) were thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd_2(dba)_3$ (0.05 eq.), and the mixture was heated to 100 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried overNa_2SO_4, concentrated, and purified by flash column chromatograph to give the intermediate **60C**.

7-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4(1H)-one

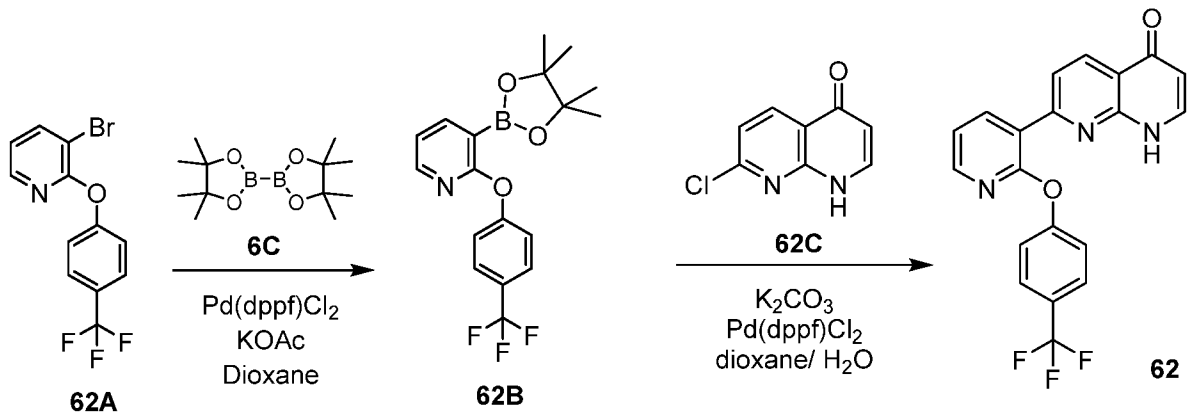
[00330] Intermediate **60C** (14 mg, 0.05 mmol, 1 eq.) and (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**, 14 mg, 0.05 mmol, 1 eq.) were suspended in 1:4 K_2CO_3 2M/dioxane (0.1 mL/ 0.4MmL 0.1M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (4 mg, 0.1 eq.) and the reaction mixture was heated to 100 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 60**. LC-MS Calcd.: 383 ($[M+H]^+$), m/z found: 383. ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 6.26 (br d, J=7.34 Hz, 1 H) 7.63 (d, J=8.80 Hz, 2 H) 7.75 - 7.79 (m, 3 H) 8.07 - .12 (m, 2 H) 8.25 (d, J=8.44 Hz, 1 H) 8.28 - 8.32 (m, 2 H) 9.08 (s, 1 H) 12.33 (br s, 1 H).

Example 61: 7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one (Compound 61)



[00331] **Compound 61** was prepared by employing the procedure for **Compound 62** using 7-chloroquinolin-4(1H)-one (**61A**) in lieu of **62C** (10 mg, 26%). LC-MS Calcd.: 383 ([M+H]$^+$), m/z found: 383. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.35 (d, J=6.97 Hz, 1 H) 7.39 - 7.43 (m, 3 H) 7.60 - 7.66 (m, 1 H) 7.75 (dd, J=8.62, 1.65 Hz, 1 H) 7.80 (d, J=8.44 Hz, 2 H) 8.00 (d, J=1.47 Hz, 1 H) 8.13 (dd, J=7.70, 1.83 Hz, 1 H) 8.18 (d, J=7.34 Hz, 1 H) 8.23 - 8.26 (m, 2 H).

Example 62: 7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one (Compound 62)



3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(4-(trifluoromethyl)phenoxy)pyridine

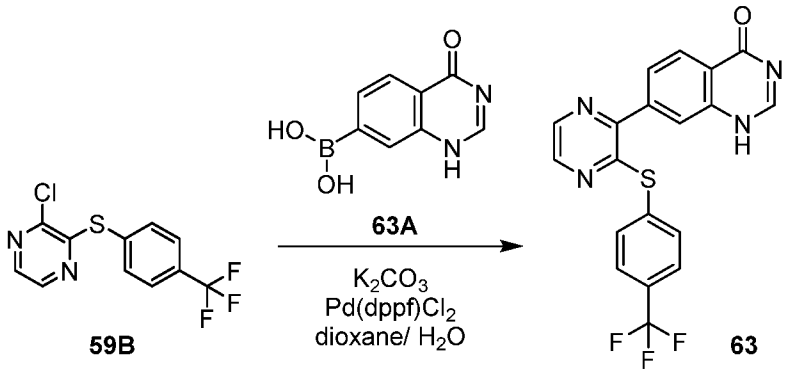
[00332] 3-Bromo-2-(4-(trifluoromethyl)phenoxy)pyridine (**62A**, 954 mg, 3 mmol, 1 eq.), **6C** (910 mg, 3.6 mmol, 1.2 eq.), and KOAc (589 mg, 6 mmol, 2 eq.) and dioxane (30 mL, 0.1M) were thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (244 mg, 0.1 eq.) and the mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layer was dried over Na_2SO_4, concentrated, and purified

by flash column chromatography to give intermediate **62B** (338 mg, 31%). LC-MS Calcd.: 366 ([M+H]$^+$), m/z found: 366.

7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one

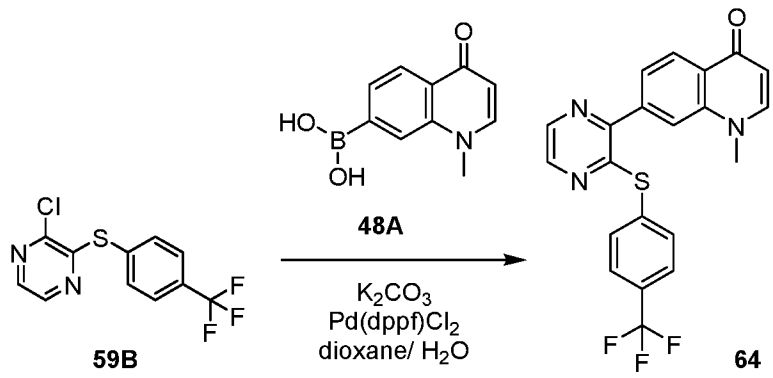
[00333] Chloro-1,8-naphthyridin-4(1H)-one (**62C**, 18 mg, 0.1 mmol, 1 eq.) and intermediate **62B** (43 mg, 0.12 mmol, 1.2 equiv.) were suspended in 1:4 K_2CO_3 2M/dioxane (0.1mL/0.4 mL, 0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (7 mg, 0.1 eq.) and the mixture was heated to 100 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 62** (7 mg, 18%). LC-MS Calcd.: 384 ([M+H]$^+$), m/z found: 384. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.15 (d, J=7.70 Hz, 1 H) 7.42 - 7.48 (m, 3 H) 7.82 (d, J=8.80 Hz, 2 H) 8.00 (br d, J=6.97 Hz, 1 H) 8.04 (d, J=8.44 Hz, 1 H) 8.31 (dd, J=4.77, 1.83 Hz, 1 H) 8.41 (dd, J=7.70, 1.83 Hz, 1 H) 8.54 (d, J=8.44 Hz, 1 H) 12.32 (br s, 1 H).

Example 63: 7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one (Compound 63)



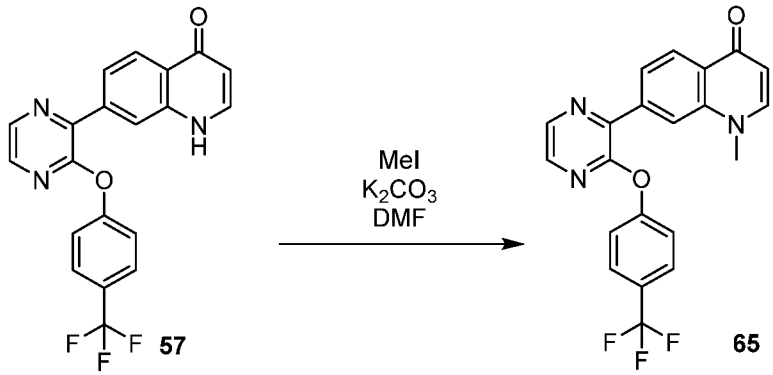
[00334] **Compound 63** was prepared by employing the procedure for **Compound 59** using 7(4-oxo-1,4-dihydroquinazolin-7-yl)boronic acid (**63A**) in lieu of **46A** (10 mg, 26%). LC-MS Calcd.: 401 ([M+H]+), m/z found: 401.

Example 64: 1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one (Compound 64)



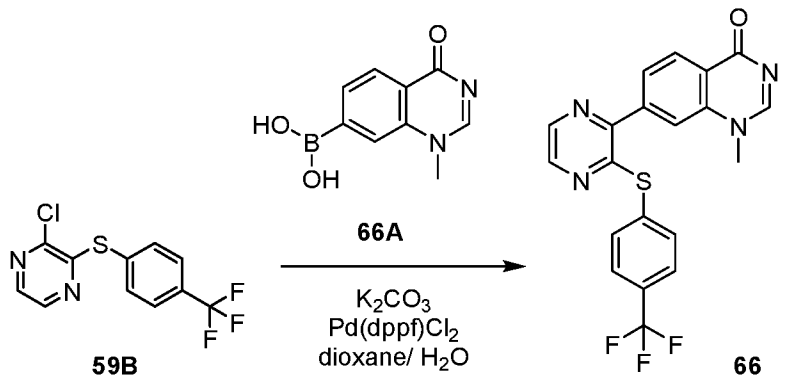
[00335] **Compound 64** was prepared by employing the procedure for **Compound 59** using (1-methyl-4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**48A**) in lieu of **46A**. LC-MS Calcd.: 414.4 ([M+H]+), m/z found: 414.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.32 - 3.34 (m, 5 H) 3.88 (s, 3 H) 6.13 (d, *J*=7.70 Hz, 1 H) 7.55 (br d, *J*=6.97 Hz, 1 H) 7.71 - 7.80 (m, 5 H) 7.98 - 8.02 (m, 1 H) 8.06 (d, *J*=7.70 Hz, 1 H) 8.32 (d, *J*=8.44 Hz, 1 H) 8.51 (d, *J*=2.20 Hz, 1 H) 8.62 (d, *J*=2.20 Hz, 1 H).

Example 65: 1-Methyl-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one (Compound 65)



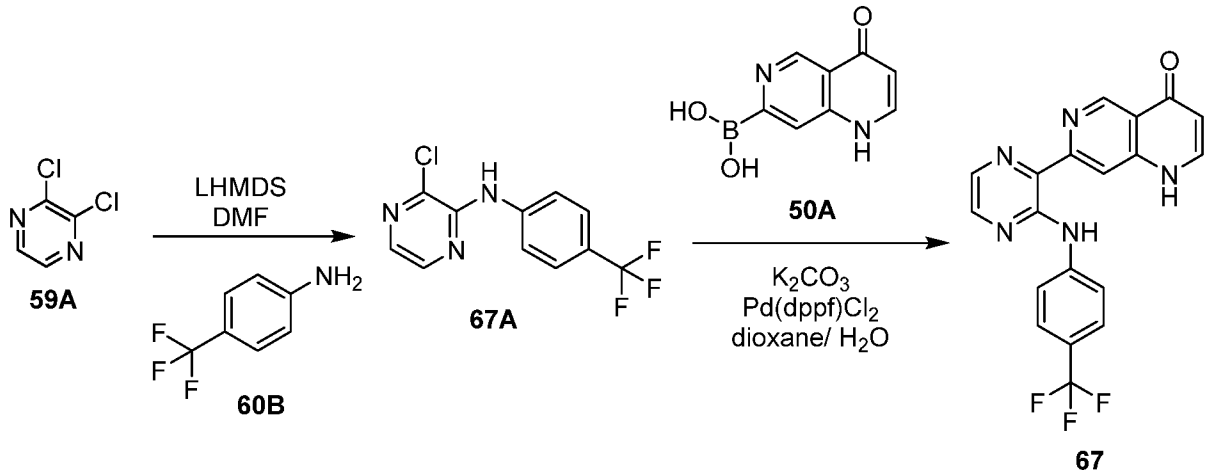
[00336] **Compound 57** (1 eq.), iodomethane (1 eq.), K_2CO_3 (2 eq.), and DMF were stirred at room temperature for 5 hr. The reaction mixture was diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and by flash column chromatography (DCM/EtOAc gradient) to afford **Compound 65** (4.7 mg, 27%).

Example 66: 1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one (Compound 66)



[00337] **Compound 66** was prepared by employing the procedure for **Compound 59** using (1-methyl-4-oxo-1,4-dihydroquinazolin-7-yl)boronic acid (**66A**) in lieu of **46A**. LC-MS Calcd.: 414.4 ([M+H]+), m/z found: 414.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.32 - 3.34 (m, 5 H) 3.88 (s, 3 H) 6.13 (d, *J*=7.70 Hz, 1 H) 7.55 (br d, *J*=6.97 Hz, 1 H) 7.71 - 7.80 (m, 5 H) 7.98 - 8.02 (m, 1 H) 8.06 (d, *J*=7.70 Hz, 1 H) 8.32 (d, *J*=8.44 Hz, 1 H) 8.51 (d, *J*=2.20 Hz, 1 H) 8.62 (d, *J*=2.20 Hz, 1 H).

Example 67: 7-(3-((4-(trifluoromethyl)phenyl)amino)pyrazin-2-yl)-1,6-naphthyridin-4(1H)-one (Compound 67)



3-Chloro-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine

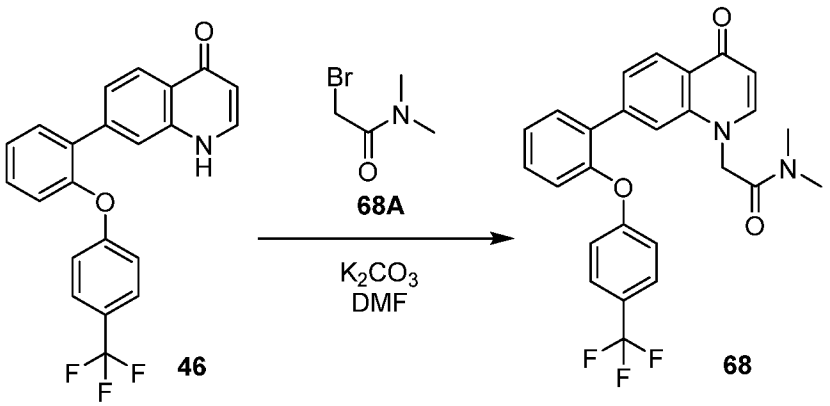
[00338] 4-(Trifluoromethyl)aniline (**60B**, 0.13 mL, 1 mmol, 1 eq.) in DMF (3 mL, 0.33M) was cooled to 0 °C. LHMDS (1M) (1.05 mL 1.05 mmol, 1.05 eq.) was added dropwise and the reaction mixture was stirred 1 hr. 2,3-Dichloropyrazine (**59A**, 163 mg, 1.1 mmol, 1.1 eq.) was added and the reaction mixture was heated to 90 °C until LC-MS indicated the consumption of start material. The reaction mixture was cooled to room temperature, quenched with NH_4Cl, diluted with EtOAc,

and washed with H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography to give intermedidate **67A** (30 mg, 10%). LC-MS Calcd.: 274 ([M+H]$^+$), m/z found: 274.

7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one

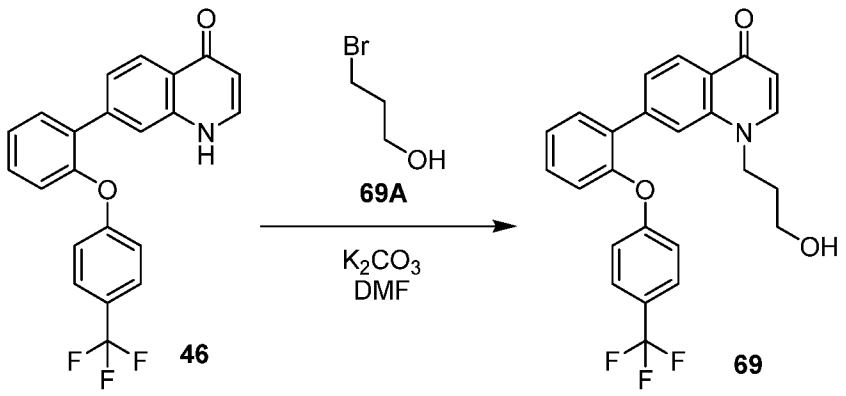
[00339] Intermedidate **67A** (1 eq.) and (4-oxo-1,4-dihydro-1,6-naphthyridin-7-yl)boronic acid (**50A**, 1.2 equiv.) were suspended in K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq.) and the mixture was heated to 100 °C until LC-MS indicated the consumption of start material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 67**. LC-MS Calcd.: 384 ([M+H]+), m/z found: 384.0.

Example 68: *N,N*-Dimethyl-2-(4-oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)acetamide (Compound 68)



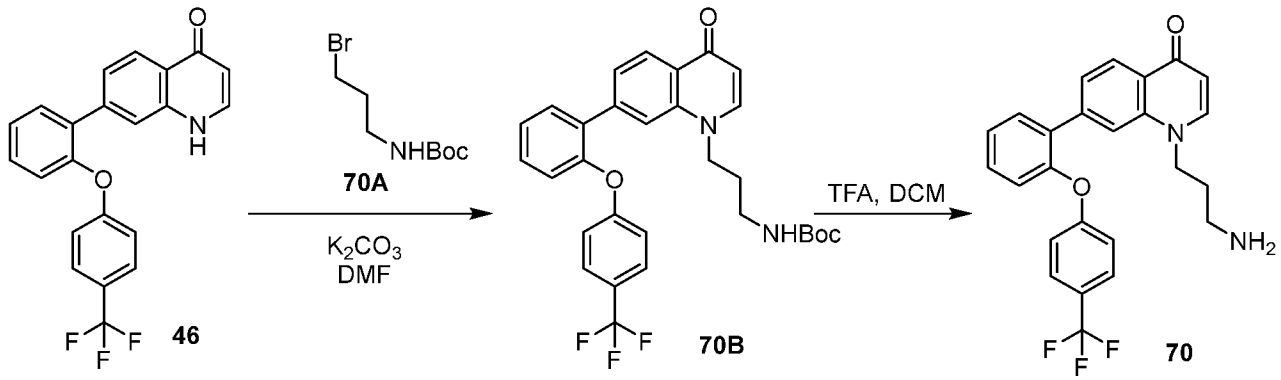
[00340] **Compound 46** (19 mg, 0.05 mmol, 1 eq.), 2-bromo-N,N-dimethylacetamide (**68A**, 0.055 mmol, 1.1 eq.), K_2CO_3 (14 mg, 0.1 mmol, 2 eq.), and DMF (0.5 mL) were stirred at room temperature for 5 hr. The reaction mixture was diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by flash column chromatography (O-alkylation is less polar than N-alkylation) (DCM/EtOAc gradient) to afford **Compound 68**. LCMS Calcd.: 539 ([M+H]$^+$), m/z found: 539.

Example 69: 1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one (Compound 69)



[00341] **Compound 69** was prepared by employing the procedure for **Compound 68** using 3-bromopropan-1-ol (**69A**) in lieu of **68A** (4.6 mg, 21%). LC-MS Calcd.: 440 ($[M+H]^+$), m/z found: 440. ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 0.83 - 0.91 (m, 2 H) 1.76 (quin, J=6.49 Hz, 2 H) 4.23 (t, J=6.96 Hz, 2 H) 6.05 (d, J=7.91 Hz, 1 H) 7.08 (d, J=8.66 Hz, 2 H) 7.25 (dd, J=8.09, 0.94 Hz, 1 H) 7.46 (td, J=7.53, 1.13 Hz, 1 H) 7.50 (dd, J=8.47, 1.32 Hz, 1 H) 7.55 (t, J=7.76 Hz, 1 H) 7.66 (d, J=8.66 Hz, 2 H) 7.69 (dd, J=7.53, 1.51 Hz, 1 H) 7.77 (d, J=1.13 Hz, 1 H) 7.94 (d, J=7.53 Hz, 1 H) 8.17 (d, J=8.66 Hz, 1 H).

Example 70: 1-(3-Aminopropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one (Compound 70)



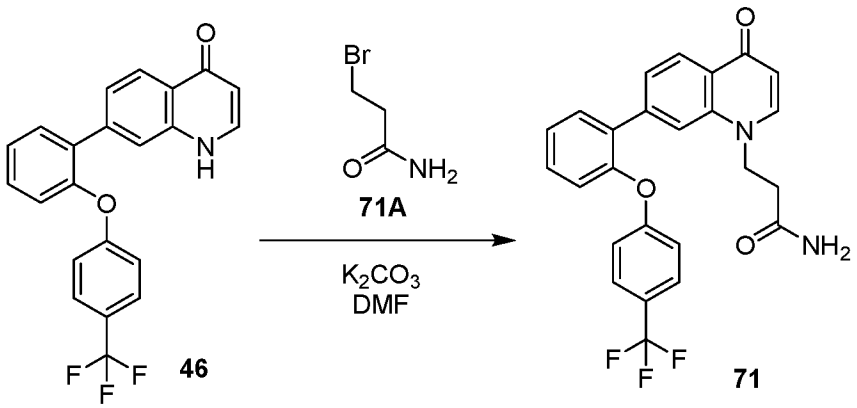
Tert-butyl (3-(4-oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)propyl)carbamate

[00342] Intermediate **70B** was prepared by employing the procedure for **Compound 68** using tert-butyl (3-bromopropyl)carbamate (**70A**) in lieu of **68A**. LC-MS Calcd.: 539 ($[M+H]^+$), m/z found: 539.

1-(3-Aminopropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one

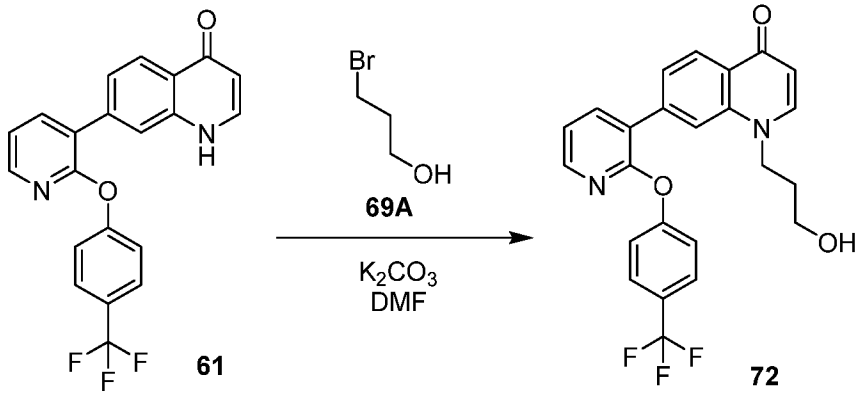
[00343] Intermediate **70B** (1 eq.) was dissolved in DCM (0.5 mL), and TFA was added (0.5 mL). The reaction mixture was stirred at room temperature for 2 hr. The reaction mixture was concentrated to afford **Compound 70** (5.3 mg, 20%, 2 steps). LC-MS Calcd.: 439 ([M+H]$^+$), m/z found: 439. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 1.98 (quin, J=7.25 Hz, 2 H) 2.79 - 2.85 (m, 2 H) 4.28 (t, J=6.96 Hz, 2 H) 6.10 (d, J=7.91 Hz, 1 H) 7.10 (d, J=8.28 Hz, 2 H) 7.26 (dd, J=8.09, 0.94 Hz, 1 H) 7.47 (td, J=7.53, 1.13 Hz, 1 H) 7.51 (dd, J=8.28, 1.51 Hz, 1 H) 7.57 (td, J=7.81, 1.69 Hz, 1 H) 7.68 (br d, J=8.66 Hz, 5 H) 7.79 (s, 1 H) 7.98 (d, J=7.91 Hz, 1 H) 8.16 (d, J=8.66 Hz, 1 H).

Example 71: 3-(4-Oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)propanamide (Compound 71)



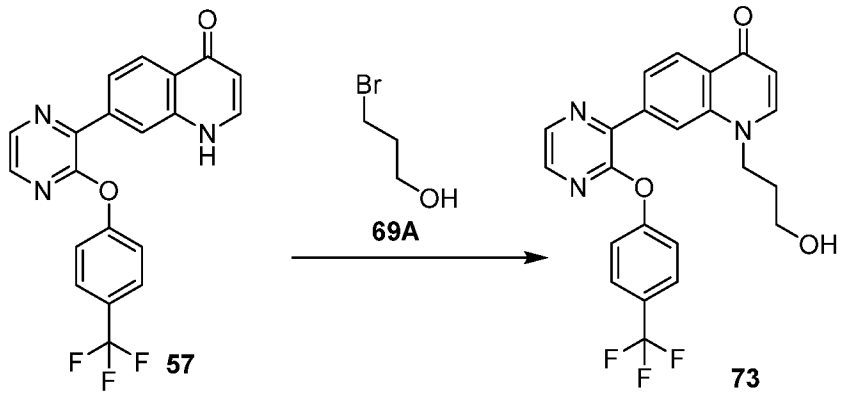
[00344] **Compound 71** was prepared by employing the procedure for **Compound 68** using 3-bromopropanamide (**71A**) in lieu of **68A**. LC-MS Calcd.: 453 ([M+H]+), m/z found: 453. ^{1}H NMR (600 MHz, DMSO-*d*6) *δ* ppm 2.53-2.55 (t, *J*=6.59 Hz, 2 H) 4.40 (t, *J*=6.59 Hz, 2 H) 6.02 (d, *J*=7.91 Hz, 1 H) 7.00 (br s, 1 H) 7.10 (m, *J*=8.66 Hz, 2 H) 7.25 (dd, *J*=8.28, 1.13 Hz, 1 H) 7.40 (br s, 1 H) 7.46 (td, *J*=7.53, 1.13 Hz, 1 H) 7.51 (dd, *J*=8.28, 1.13 Hz, 1 H) 7.56 (td, *J*=7.81, 1.69 Hz, 1 H) 7.67 (m, *J*=8.66 Hz, 2 H) 7.73 (dd, *J*=7.72, 1.69 Hz, 1 H) 7.78 (s, 1 H) 7.91 (d, *J*=7.53 Hz, 1 H) 8.14 (d, *J*=8.28 Hz, 1 H).

Example 72: 1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one (Compound 72)



[00345] **Compound 61** (1 eq.) 3-bromopropan-1-ol (**69A**, 2 eq.), K_2CO_3 (2 eq.), and DMF (0.3M) were stirred at rt for 16 hr. The reaction mixture was diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried over Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 72**. LC-MS mass calcd., $C_{24}H_{19}F_3N_2O_3$, 440. m/z found, 441 $[M+H]^+$.^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.90 (quin, *J*=6.42 Hz, 2 H) 3.40 (t, *J*=5.87 Hz, 2 H) 4.40 (br t, *J*=7.06 Hz, 2 H) 6.22 (d, *J*=7.52 Hz, 1 H) 7.37 - 7.44 (m, 3 H) 7.53 - 7.59 (m, 2 H) 7.60 - 7.65 (m, 3 H) 7.74 (dd, *J*=8.44, 1.28 Hz, 1 H) 7.78 (d, *J*=8.62 Hz, 2 H) 8.08 - 8.12 (m, 2 H) 8.15 (dd, *J*=7.34, 1.83 Hz, 1 H) 8.24 (dd, *J*=4.95, 1.83 Hz, 1 H) 8.29 (d, *J*=8.44 Hz, 1 H).

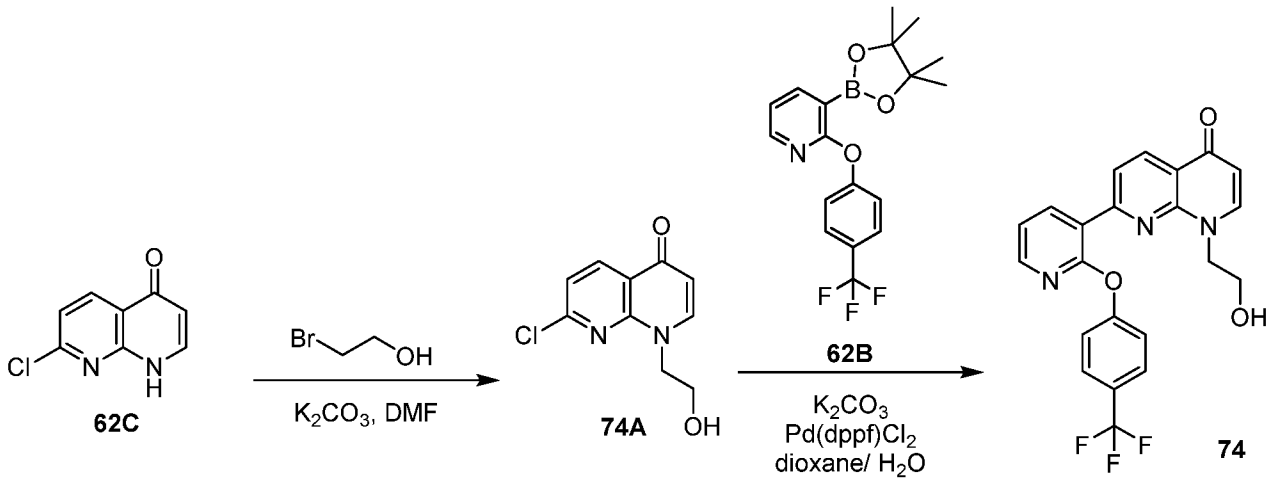
Example 73: 1-(3-Hydroxypropyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one (Compound 73)



[00346] **Compound 57** (1 eq.), 3-bromopropan-1-ol (**69A**, 2 eq.), K_2CO_3 (2 eq.), and DMF were stirred at room temperature for 5 hr. The reaction mixture was diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography (O-alkylation is less polar than N-alkylation) (DCM/EtOAc gradient) to afford **Compound 73** (4.7 mg, 27%). LC-MS Calcd.: 442 ($[M+H]^+$),

m/z found: 442. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 1.88 - 1.94 (m, 2 H) 3.38 - 3.41 (m, 7 H) 4.33 - 4.39 (m, 2 H) 6.14 (d, J=7.34 Hz, 1 H) 7.56 (d, J=8.44 Hz, 2 H) 7.85 (d, J=8.44 Hz, 2 H) 8.02 - 8.06 (m, 2 H) 8.28 - 8.34 (m, 2 H) 8.46 (d, J=1.10 Hz, 1 H) 8.63 (d, J=2.57 Hz, 1 H).

Example 74: 1-(2-Hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one (Compound 74)

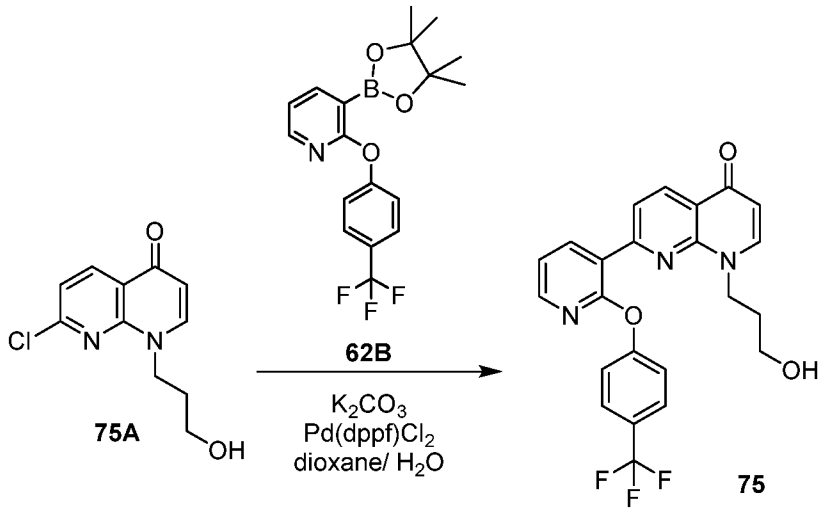


7-Chloro-1-(2-hydroxyethyl)-1,8-naphthyridin-4(1H)-one

7-Chloro-1,8-naphthyridin-4(1H)-one (**62C**, 722 mg, 4 mmol, 1 eq.), 2-bromoethan-1-ol (0.57 mL, 8 mmol, 2 eq.), K_2CO_3 (1.1 g, 8 mmol, 2 eq.), and DMF (13 mL, 0.3M) were stirred at room temperature for 16 hr. The reaction mixture was diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography to give intermediate **74A** (251 mg, 28%). LC-MS Calcd.: 225 ($[M+H]^+$), m/z found: 225.

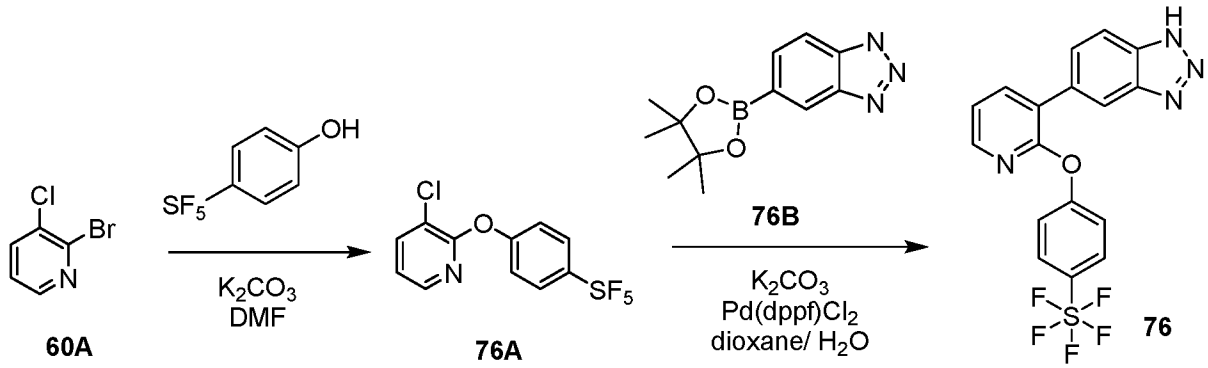
[00347] **Compound 74** was prepared by employing the procedure for **Compound 62** using intermediate **74A** in lieu of **62C** (6 mg, 7%). LCMS Calcd.: 428 ($[M+H]^+$), m/z found: 428. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 3.76 (t, J=5.32 Hz, 2 H) 4.45 (t, J=5.50 Hz, 2 H) 6.16 (d, J=7.70 Hz, 1 H) 7.42 - 7.46 (m, 3 H) 7.81 (d, J=8.44 Hz, 2 H) 8.10 (dd, J=7.89, 2.38 Hz, 2 H) 8.31 (dd, J=4.77, 1.83 Hz, 1 H) 8.48 (dd, J=7.70, 1.83 Hz, 1 H) 8.60 (d, J=8.44 Hz, 1 H).

Example 75: 1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one (Compound 75)



[00348] **Compound 75** was prepared by employing the procedure for **Compound 74** using 7-chloro-1-(3-hydroxypropyl)-1,8-naphthyridin-4(1H)-one (**75A**) in lieu of **74A** (3 mg, 3%). LCMS Calcd.: 442 ([M+H]$^+$), m/z found: 442. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 1.91 - 1.98 (m, 2 H) 3.42 - 3.48 (m, 7 H) 4.47 (t, J=6.97 Hz, 2 H) 6.17 (d, J=7.70 Hz, 1 H) 7.43 - 7.47 (m, 3 H) 7.81 (d, J=8.80 Hz, 2 H) 8.10 - 8.17 (m, 2 H) 8.30 - 8.32 (m, 1 H) 8.52 - 8.55 (m, 1 H) 8.59 (d, J=8.44 Hz, 1 H).

Example 76: 5-(2-(4-(Pentafluoro-λ^6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole (Compound 76)



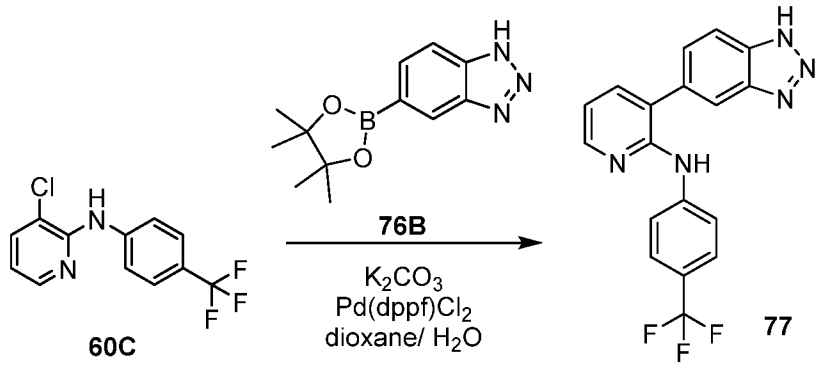
3-Chloro-2-(4-(pentafluoro-λ^6-sulfaneyl)phenoxy)pyridine

[00349] 2-Bromo-3-chloropyridine (**60A**, 1 eq.), 4-(pentafluoro-λ^6-sulfaneyl)phenol (1 eq.), K_2CO_3 (1.2 eq.), and DMF (0.3 M) were stirred at 100 °C for 16 hr. The reaction mixture was added to rapidly stirring water, and the solid was filtered to give intermediate **76A**, which was used in the next step without further purification.

5-(2-(4-(Pentafluoro-λ^6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole

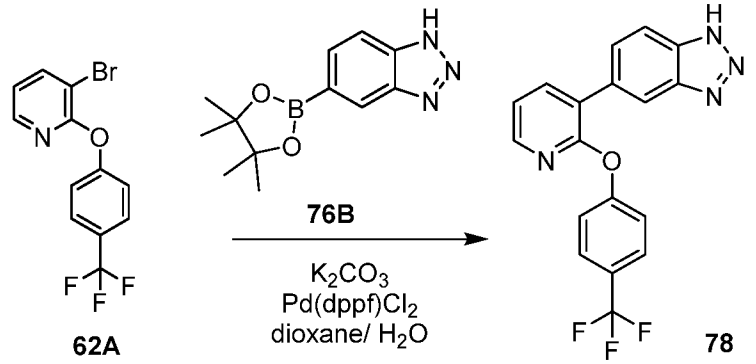
[00350] Intermediate **76A** (1 eq.) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**76B**, 1.2 equiv.) were suspended in K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq.) and the reaction mixture was heated to 100 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 76**. LC-MS Calcd.: 415 ([M+H]+), m/z found: 415.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.37 - 7.42 (m, 3 H) 7.75 (br d, *J*=8.44 Hz, 1 H) 7.92 - 7.97 (m, 2 H) 8.00 (br d, *J*=8.07 Hz, 1 H) 8.11 (dd, *J*=7.70, 1.83 Hz, 1 H) 8.18 (m, 1H) 8.22 (dd, *J*=4.77, 1.83 Hz, 1 H).

Example 77: 3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine (Compound 77)



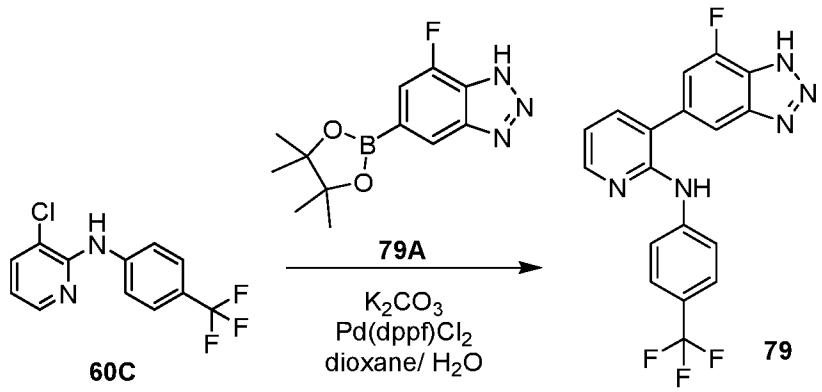
[00351] **Compound 77** was prepared by employing the procedure for **Compound 60** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**76B**) in lieu of **46A**. LC-MS Calcd.: 356 ([M+H]+), m/z found: 356. ^{1}H NMR (600 MHz, DMSO-*d*6) *δ* ppm 3.93 (s, 1 H) 7.07 - 7.11 (m, 1 H) 7.48 - 7.58 (m, 3 H) 7.66 - 7.76 (m, 3 H) 8.00 (br s, 2 H) 8.29 (dd, J=5.14, 1.83 Hz, 1 H) 8.33 (s, 1 H).

Example 78: 5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole (Compound 78)



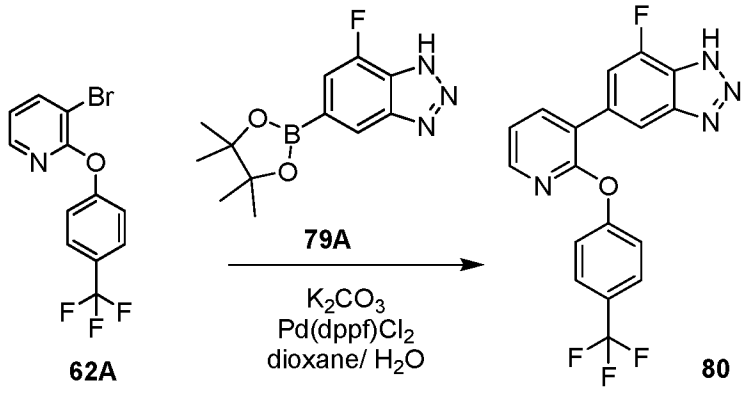
[00352] **Compound 78** was prepared by employing the procedure for **Compound 76** using intermediate **62A** in lieu of **76A**. LC-MS Calcd.: 357 ([M+H]$^+$), m/z found: 357.0.

Example 79: 3-(7-Fluoro-1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine (Compound 79)



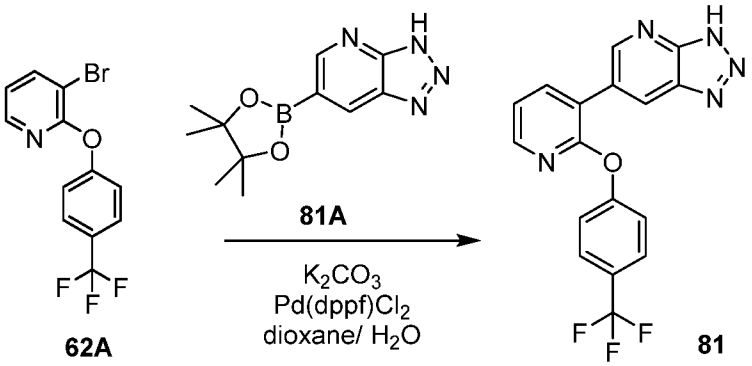
[00353] **Compound 79** was prepared by employing the procedure for **Compound 60** using 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**79A**) in lieu of **46A**. LC-MS Calcd.: 374 ([M+H]+), m/z found: 374. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.07 - 7.10 (m, 1 H) 7.35 (br d, J=11.37 Hz, 1 H) 7.55 (d, J=8.80 Hz, 2 H) 7.71 - 7.75 (m, 3 H) 7.75 - 7.80 (m, 1 H) 8.29 (dd, J=5.14, 1.83 Hz, 1 H) 8.40 (s, 1 H).

Example 80: 7-Fluoro-5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole (Compound 80)



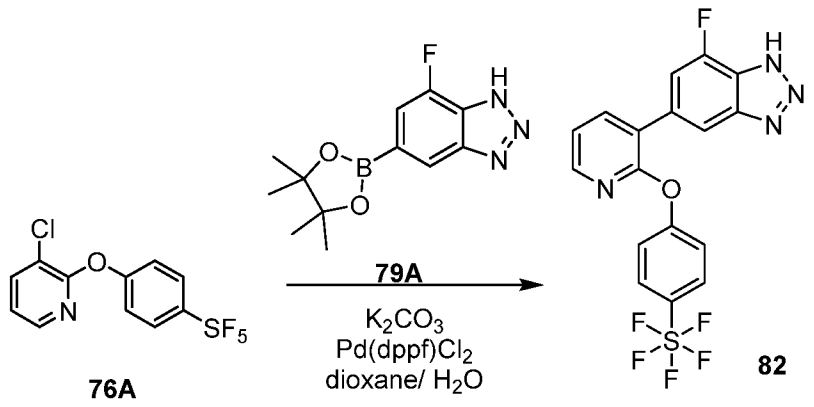
[00354] **Compound 80** was prepared by employing the procedure for **Compound 78** using 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**79A**) in lieu of **76B**. LC-MS mass calcd., C18H10F4N4O, 374. m/z found, 375 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.37 (dd, J=7.34, 4.77 Hz, 1 H) 7.42 (d, J=8.44 Hz, 2 H) 7.62 (br d, J=11.37 Hz, 1 H) 7.79 (d, J=8.80 Hz, 2 H) 8.00 (br s, 1 H) 8.13 (dd, J=7.52, 2.02 Hz, 1 H) 8.22 (dd, J=5.14, 1.83 Hz, 1 H).

Example 81: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (Compound 81)



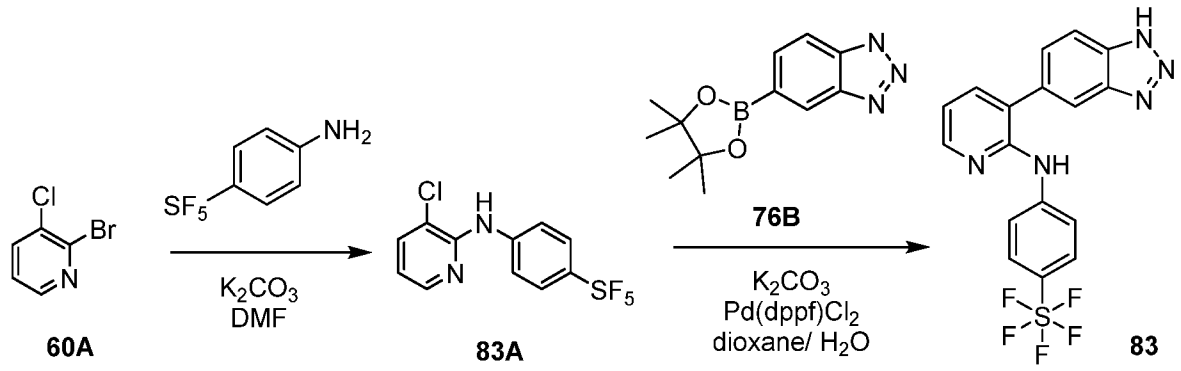
[00355] **Compound 81** was prepared by employing the procedure for **Compound 78** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (**81A**) in lieu of **76B**. LC-MS mass calcd., $C_{17}H_{10}F_3N_5O$, 357. m/z found, 358 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 7.36 - 7.43 (m, 3 H) 7.78 (d, J=8.44 Hz, 2 H) 8.14 (dd, J=7.52, 1.65 Hz, 1 H) 8.21 (dd, J=4.77, 1.83 Hz, 1 H) 8.55 (br s, 1 H) 8.82 (br s, 1 H).

Example 82: 7-Fluoro-5-(2-(4-(pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[*d*][1,2,3]triazole (Compound 82)



[00356] **Compound 82** was prepared by employing the procedure for **Compound 76** using 7-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**79A**) in lieu of **76B**. LC-MS mass calcd.: 432.0, m/z found: 433.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.37 - 7.41 (m, 1 H) 7.42 (d, *J*=9.17 Hz, 2 H) 7.59 - 7.66 (m, 1 H) 7.94 - 7.98 (m, 2 H) 8.13 (dd, *J*=7.34, 1.83 Hz, 1 H) 8.23 (dd, *J*=4.95, 2.02 Hz, 1 H).

Example 83: 3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 83)



3-Chloro-N-(4-(pentafluoro- λ⁶-sulfaneyl)phenyl)pyridin-2-amine

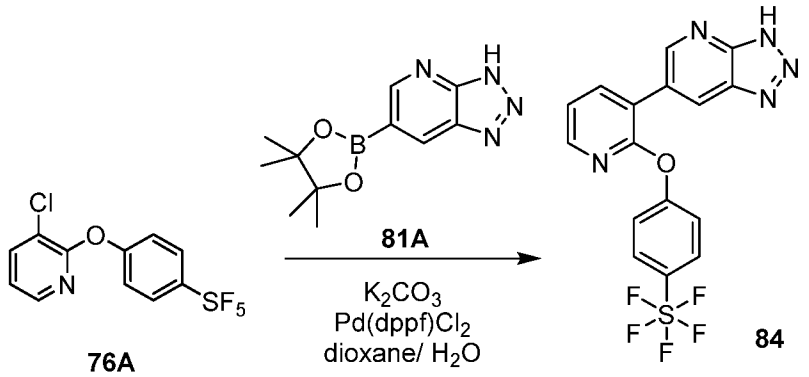
[00357] Bromo-3-chloropyridine (1 eq.),4-(pentafluoro-λ⁶-sulfaneyl)aniline (1 eq.), K_2CO_3 (1.2 eq.), and DMF (0.3M) were stirred at 100 °C for 16 hr. The reaction mixture was added to rapidly stirring water, and the solid was filtered to give intermediate **83A**, which was used in the next step without further purification.

3-(1*H*-benzo[*d*][1,2,3]triazol-5-yl)-*N*-(4-(pentafluoro- λ⁶-sulfaneyl)phenyl)pyridin-2-amine

[00358] Intermediate **83A** (1 eq.) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d][1,2,3]triazole (**76B**, 1.2 equiv.) were suspended in K_2CO_3 2M/dioxane (0.2 M) and

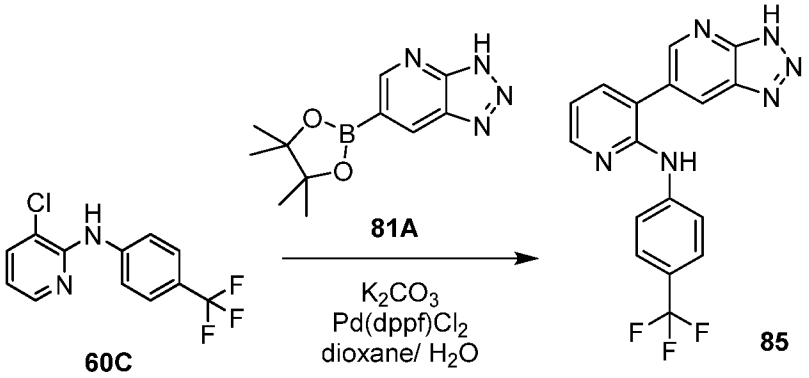
thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq.) and the mixture was heated to 100 °C until LC-MS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The combined organic layer was dried with Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 83**. LC-MS Calcd.: 414 ([M+H]+), m/z found: 414.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.12 (dd, *J*=7.34, 4.77 Hz, 1 H) 7.42 - 7.55 (m, 1 H) 7.63 - 7.74 (m, 6 H) 8.0 (m, 1H) 8.30 (dd, *J*=5.14, 1.83 Hz, 1 H) 8.46 (s, 1 H) 15.77 (br s, 1 H).

Example 84: 6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (Compound 84)



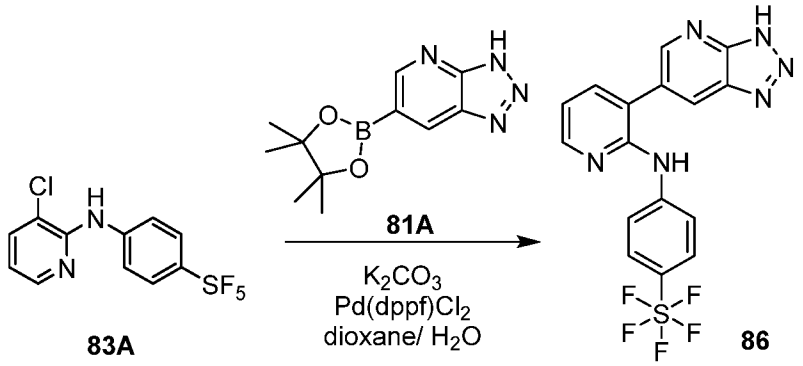
[00359] **Compound 84** was prepared by employing the procedure for **Compound 76** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (**81A**) in lieu of **76B**. LC-MS Calcd.: 416 ([M+H]+), m/z found: 416. ^{1}H NMR (600 MHz, DMSO-*d*6) *δ* ppm 7.41 (dd, J=7.52, 4.95 Hz, 1 H) 7.44 (d, J=8.80 Hz, 2 H) 7.95 - 7.98 (m, 2 H) 8.16 - 8.21 (m, 1 H) 8.25 8.29 (m, 1 H) 8.73 (br d, J=1.83 Hz, 1 H) 9.01 - 9.04 (m, 1 H).

Example 85: 3-(3H-[1,2,3]Triazolo[4,5-b]pyridin-6-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine (Compound 85)



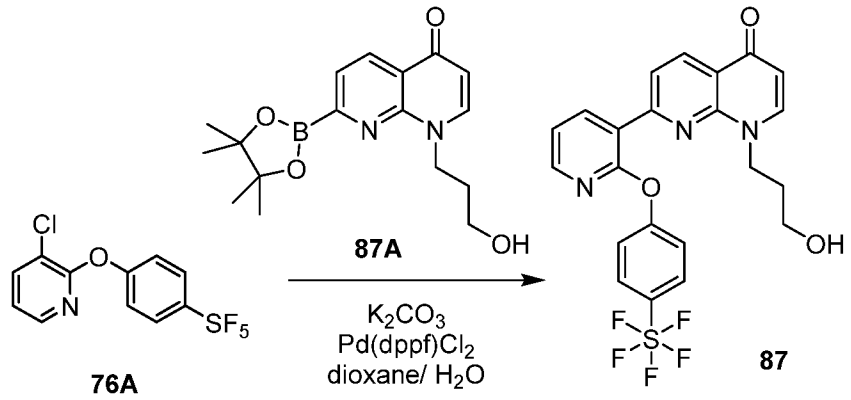
[00360] **Compound 85** was prepared by employing the procedure for **Compound 60** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (**81A**) in lieu of **46A**. LC-MS Calcd.: 357 ([M+H]+), m/z found: 357. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.12 (dd, J=7.34, 4.77 Hz, 1 H) 7.55 (d, J=8.80 Hz, 2 H) 7.71 (d, J=8.44 Hz, 2 H) 7.77 (dd, J=7.52, 1.65 Hz, 1 H) 8.32 (dd, J=4.95, 2.02 Hz, 1 H) 8.52 (s, 1 H) 8.53 (d, J=7.19 Hz, 1 H) 8.74 (d, J=1.83 Hz, 1 H).

Example 86: 6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (Compound 83)



[00361] **Compound 86** was prepared by employing the procedure for **Compound 83** using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine (**81A**) in lieu of **76B**. LCMS Calcd.: 415 ([M+H]+), m/z found: 415.0.

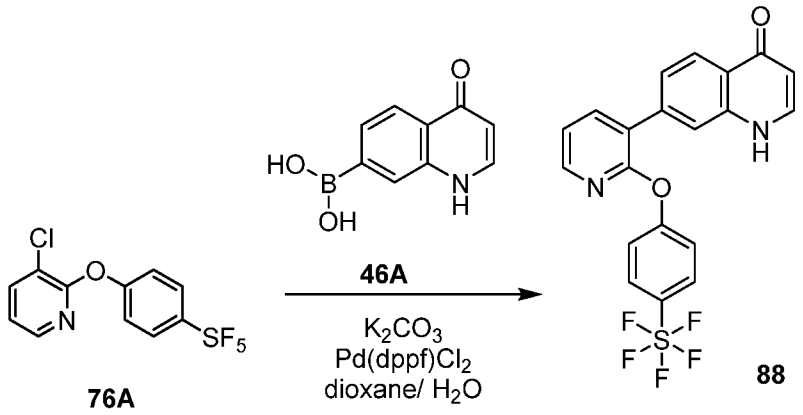
Example 87: 1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one (Compound 87)



[00362] **Compound 87** was prepared by employing the procedure for **Compound 76** using 1-(3-hydroxypropyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,8-naphthyridin-4(1H)-one (**87A**) in lieu of **76B**. LC-MS Calcd.: 500 ([M+H]+), m/z found: 500. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 1.91 - 2.00 (m, 2 H) 3.43 (q, J=5.87 Hz, 2 H) 4.46 (t, J=6.97 Hz, 2 H) 4.64 (t, J=4.95 Hz, 1 H)

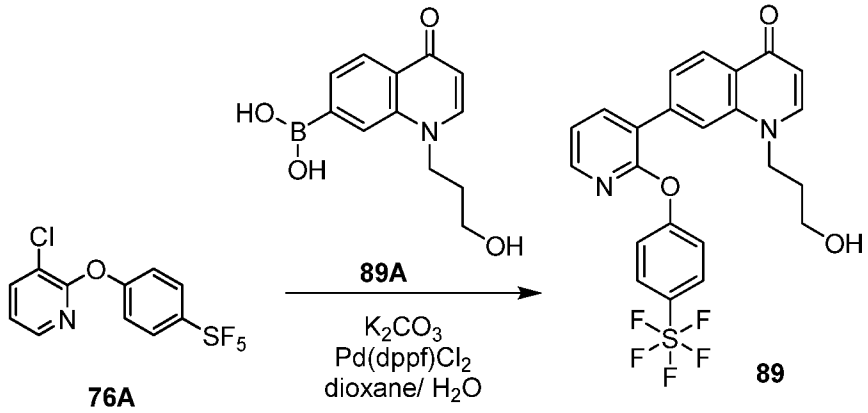
6.17 (d, J=7.89 Hz, 1 H) 7.44 - 7.48 (m, 3 H) 7.98 (d, J=9.17 Hz, 2 H) 8.09 (d, J=8.25 Hz, 1 H) 8.15 (d, J=7.89 Hz, 1 H) 8.32 (dd, J=4.68, 1.74 Hz, 1 H) 8.54 (dd, J=7.52, 1.83 Hz, 1 H) 8.59 (d, J=8.25 Hz, 1 H).

Example 88: 7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one (Compound 88)



[00363] **Compound 88** was prepared by employing the procedure for **Compound 76** using (4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**46A**) in lieu of **76B**. LC-MS Calcd.: 441 ([M+H]+), m/z found: 441. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.06 (d, J=7.34 Hz, 1 H) 7.38 - 7.42 (m, 3 H) 7.60 (dd, J=8.34, 1.56 Hz, 1 H) 7.85 (d, J=1.47 Hz, 1 H) 7.91 7.94 (m, 1 H) 7.95 - 7.99 (m, 2 H) 8.11 (dd, J=7.52, 1.83 Hz, 1 H) 8.16 (d, J=8.44 Hz, 1 H) 8.25 (dd, J=4.77, 1.83 Hz, 1 H) 11.83 (br s, 1 H).

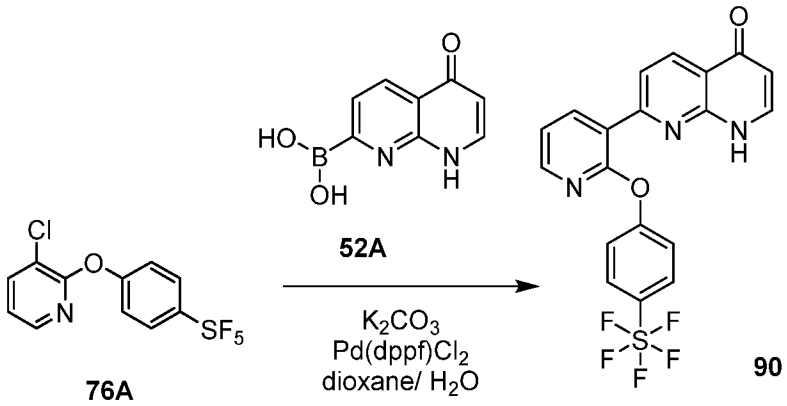
Example 89: 1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro- λ^6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one (Compound 89)



[00364] **Compound 89** was prepared by employing the procedure for **Compound 76** using (1-(3-hydroxypropyl)-4-oxo-1,4-dihydroquinolin-7-yl)boronic acid (**89A**) in lieu of **76B**. LC-MS Calcd.: 499 ([M+H]+), m/z found: 499. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 1.89 (quin,J=6.51

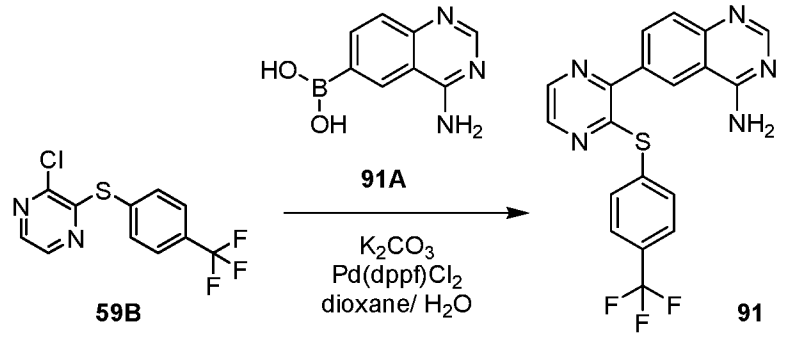
Hz, 2 H) 3.40 (t, J=5.87 Hz, 2 H) 4.38 (t, J=7.06 Hz, 2 H) 6.18 (d, J=7.52 Hz, 1 H) 7.39 7.44 (m, 3 H) 7.71 (dd, J=8.34, 1.38 Hz, 1 H) 7.94 - 7.97 (m, 2 H) 8.06 - 8.09 (m, 2 H) 8.16 (dd, J=7.52, 1.83 Hz, 1 H) 8.25 (dd, J=4.77, 1.83 Hz, 1 H) 8.28 (d, J=8.25 Hz, 1 H).

Example 90: 7-(2-(4-(Pentafluoro-λ^6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one (Compound 90)



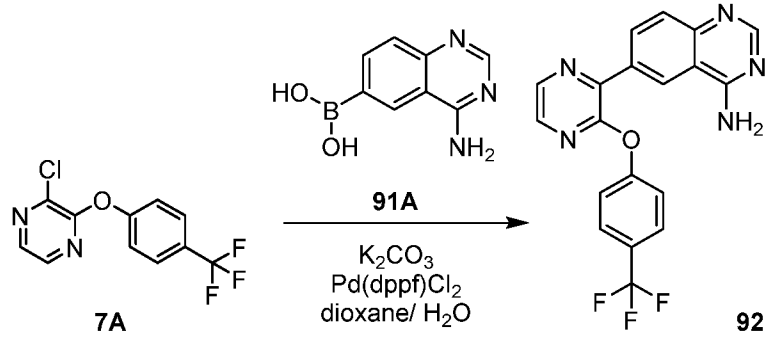
[00365] **Compound 90** was prepared by employing the procedure for **Compound 76** using (5-oxo-5,8-dihydro-1,8-naphthyridin-2-yl)boronic acid (**52A**) in lieu of **76B**. LC-MS mass calcd., $C_{19}H_{12}F_5N_3O_2S$, 441. m/z found, 442 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 6.15 (d, *J*=7.52 Hz, 1 H) 7.43 - 7.47 (m, 3 H) 7.97 - 8.01 (m, 3 H) 8.03 (d, *J*=8.25 Hz, 1 H) 8.30 - 8.33 (m, 1 H) 8.40 - 8.43 (m, 1 H) 8.54 (d, *J*=8.25 Hz, 1 H) 12.30 (br s, 1 H).

Example 91: 6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine (Compound 91)



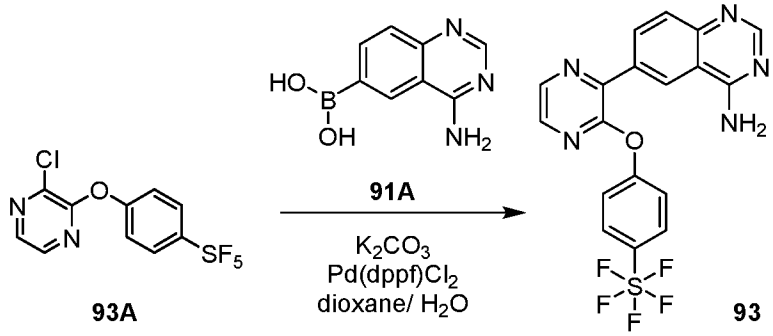
[00366] **Compound 91** was prepared by employing the procedure for **Compound 59** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **46A**. LC-MS Calcd.: 399.1 m/z found: 400.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 7.70 (d, *J*=8.25 Hz, 2 H) 7.78 (d, *J*=8.25 Hz, 2 H) 7.90 (d, *J*=8.62 Hz, 1 H) 8.34 (br d, *J*=8.25 Hz, 1 H) 8.53 (d, *J*=2.57 Hz, 1 H) 8.64 (d, *J*=2.57 Hz, 1 H) 8.74 (s, 1 H) 8.79 (br s, 1 H).

Example 92: 6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine (Compound 92)



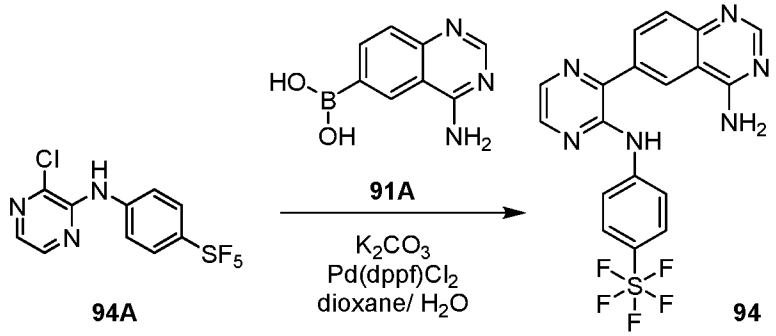
[00367] **Compound 92** was prepared by employing the procedure for **Compound 57** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **46A**. LC-MS Calcd.: 383.1, m/z found: 384.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.56 (d, *J*=8.44 Hz, 2 H) 7.87 (d, *J*=8.62 Hz, 2 H) 7.94 (d, *J*=8.80 Hz, 1 H) 8.31 (d, *J*=2.38 Hz, 1 H) 8.64 (d, *J*=2.38 Hz, 1 H) 8.72 (dd, *J*=8.80, 1.47 Hz, 1 H) 8.89 (s, 1 H) 9.09 (s, 1 H) 9.89 (br s, 1 H) 10.05 (br s, 1 H).

Example 93: 6-(3-(4-(Pentafluoro- λ^6-sulfaneyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine (Compound 93)



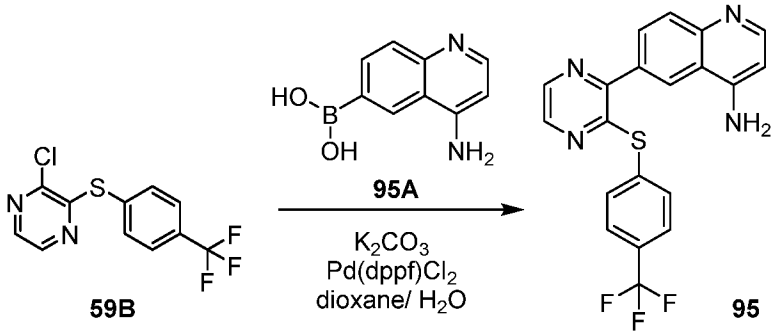
[00368] **Compound 93** was prepared by employing the procedure for **Compound 92** using intermediate **93A** in lieu of intermediate **7A**. LC-MS Calcd.: 441.1, m/z found: 441.9 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.56 (d, *J*=8.99 Hz, 2 H) 7.79 (d, *J*=8.80 Hz, 1 H) 8.02 (d, *J*=9.17 Hz, 2 H) 8.25 (d, *J*=2.57 Hz, 1 H) 8.41 (dd, *J*=8.80, 1.83 Hz, 1 H) 8.44 (s, 1 H) 8.61 (d, *J*=2.57 Hz, 1 H) 8.89 (d, *J*=1.47 Hz, 1 H).

Example 94: 6-(3-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinazolin-4-amine (Compound 94)



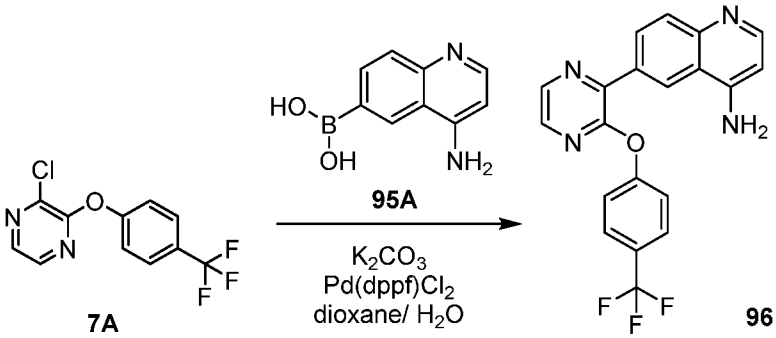
[00369] **Compound 94** was prepared by employing the procedure for **Compound 92** using intermediate **94A** in lieu of intermediate **7A**. LC-MS Calcd.: 440.1, m/z found: 441.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.69 - 7.77 (m, 2 H) 7.77 - 7.84 (m, 2 H) 7.92 (d, *J*=8.80 Hz, 1 H) 8.31 - 8.40 (m, 3 H) 8.85 (d, *J*=1.10 Hz, 1 H) 8.90 (s, 1 H) 9.13 (s, 1 H) 9.75 - 9.95 (m, 2 H).

Example 95: 6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4-amine (Compound 95)



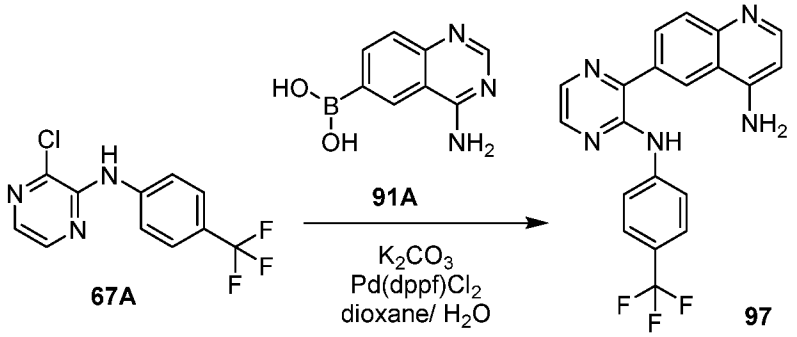
[00370] **Compound 95** was prepared by employing the procedure for **Compound 59** using (4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **46A**. LC-MS Calcd.: 399 ([M+H]+), m/z found: 399.0.

Example 96: 6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4-amine (Compound 96)



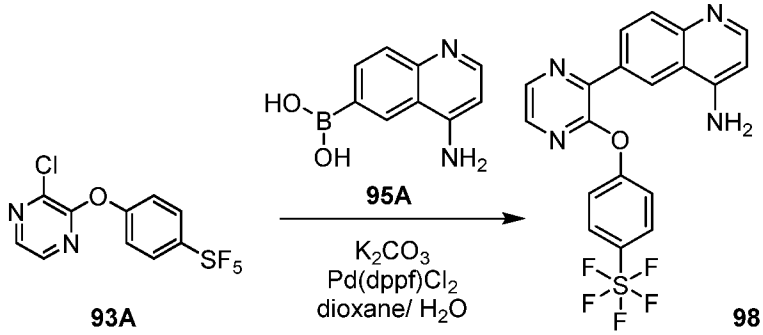
[00371] **Compound 96** was prepared by employing the procedure for **Compound 57** using 4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **46A**. LC-MS Calcd.: 382.1, m/z found: 399.0 ($[M+H]^+$).

Example 97: 6-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine (Compound 97)



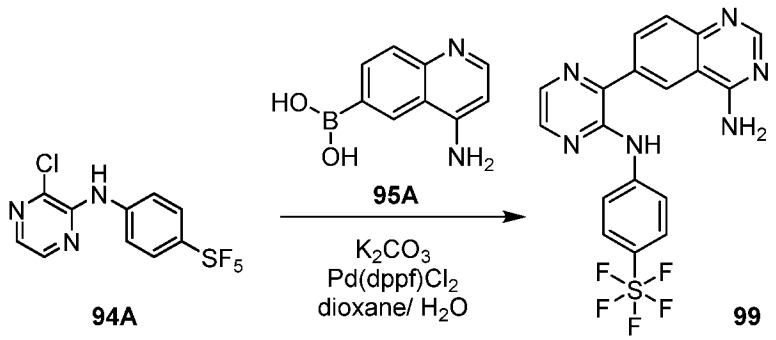
[00372] **Compound 97** was prepared by employing the procedure for **Compound 67** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **50A**. LC-MS Calcd.: 381.1 m/z found: 382.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.83 (d, *J*=6.97 Hz, 1 H) 7.62 (d, *J*=8.62 Hz, 2 H) 7.78 (d, *J*=8.44 Hz, 2 H) 7.99 (d, *J*=8.80 Hz, 1 H) 8.31 (s,2 H) 8.48 (t, *J*=6.24 Hz, 1 H) 8.83 (d, *J*=1.10 Hz, 1 H) 8.97 (s, 1 H) 9.03 (br s, 1 H) 9.07 (br s, 1 H) 13.75 (br s, 1 H).

Example 98: 6-(3-(4-(pentafluoro- λ^6-sulfaneyl)phenoxy)pyrazin-2-yl)quinolin-4-amine (Compound 98)



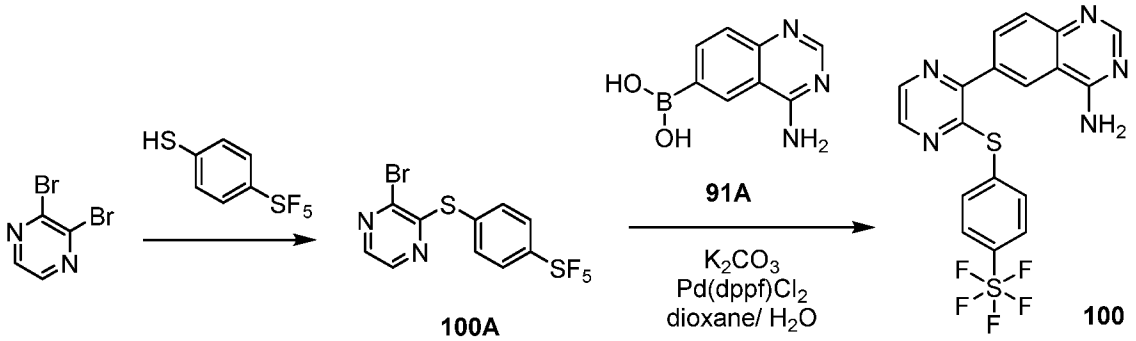
[00373] **Compound 98** was prepared by employing the procedure for **Compound 93** using intermediate **95A** in lieu of intermediate **91A**. LC-MS Calcd.: 440.1, m/z found: 441.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.67 (d, *J*=5.87 Hz, 1 H) 7.36 - 7.45 (m, 3 H) 7.86 (d, *J*=8.80 Hz, 1 H) 7.94 - 7.98 (m, 2 H) 8.06 (br d, *J*=8.25 Hz, 1 H) 8.12 (dd, *J*=7.43, 1.93 Hz, 1 H) 8.24 (dd, *J*=4.95, 1.83 Hz, 1 H) 8.38 (d, *J*=5.87 Hz, 1 H) 8.53 (s, 1 H).

Example 99: 6-(3-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine (Compound 99)



[00374] **Compound 99** was prepared by employing the procedure for **Compound 92** using intermediate **95A** in lieu of intermediate **91A**. LC-MS Calcd.: 439.1, m/z found: 440.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.85 (d, *J*=6.97 Hz, 1 H) 7.73 - 7.81 (m, 4 H) 8.01 (d, *J*=8.62 Hz, 1 H) 8.25 (dd, *J*=8.80, 1.47 Hz, 1 H) 8.34 (d, *J*=6.84 Hz, 2 H) 8.49 (br d, *J*=6.60 Hz, 1 H) 8.83 (s, 1 H) 9.08 (s, 1 H) 9.10 (s, 2 H) 13.94 (br s, 1 H).

Example 100: 6-(3-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine (Compound 100)



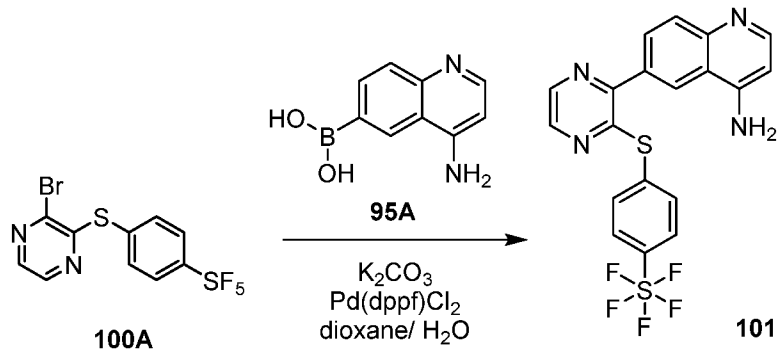
2-bromo-3-((4-(pentafluoro- λ⁶-sulfaneyl)phenyl)thio)pyrazine

[00375] 4-(pentafluoro- λ⁶-sulfaneyl)benzenethiol (472 mg, 1 eq.) was dissolved in DMF (20 mL) and cooled to 0 °C. K_2CO_3 (277 mg, 1 eq.) was slowly added followed by 2,3-dibromopyrazine (476 mg, 1 eq.). The reaction mixture was warmed to 23 °C and stirred for 2 hr. Upon completion, the reaction mixture was diluted with Et_2O (100 mL) and washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated to give intermediate **100A** (250 mg, 32 %), which was used directly without further purification. LC-MS Calcd.: 391.9, m/z found: 393 ($[M+H]^+$).

6-(3-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine

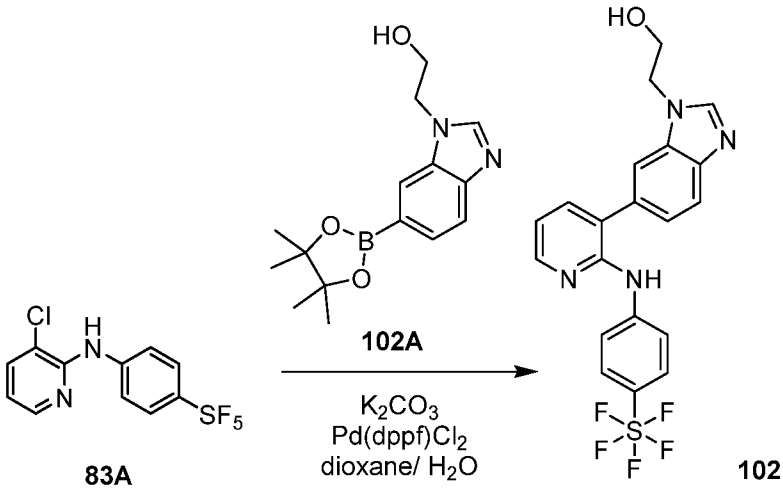
[00376] **Compound 100** was prepared by employing the procedure for **Compound 91** using 2-chloro-3-((4-(pentafluoro-l6-sulfaneyl)phenyl)thio)pyrazine (**100A**) in lieu of **59B**. LC-MS Calcd.: 457.0, m/z found: 457.9.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 6.36 - 6.64 (m, 1 H) 7.69 (d, *J*=8.62 Hz, 2 H) 7.90 - 7.95 (m, 3 H) 8.36 (dd, *J*=8.62, 1.65 Hz, 1 H) 8.57 (d, *J*=2.38 Hz, 1 H) 8.67 (d, *J*=2.57 Hz, 1 H) 8.75 (d, *J*=1.65 Hz, 1 H) 8.83 (s, 1 H) 9.58 (br s, 2 H).

Example 101: 6-(3-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine (Compound 101)



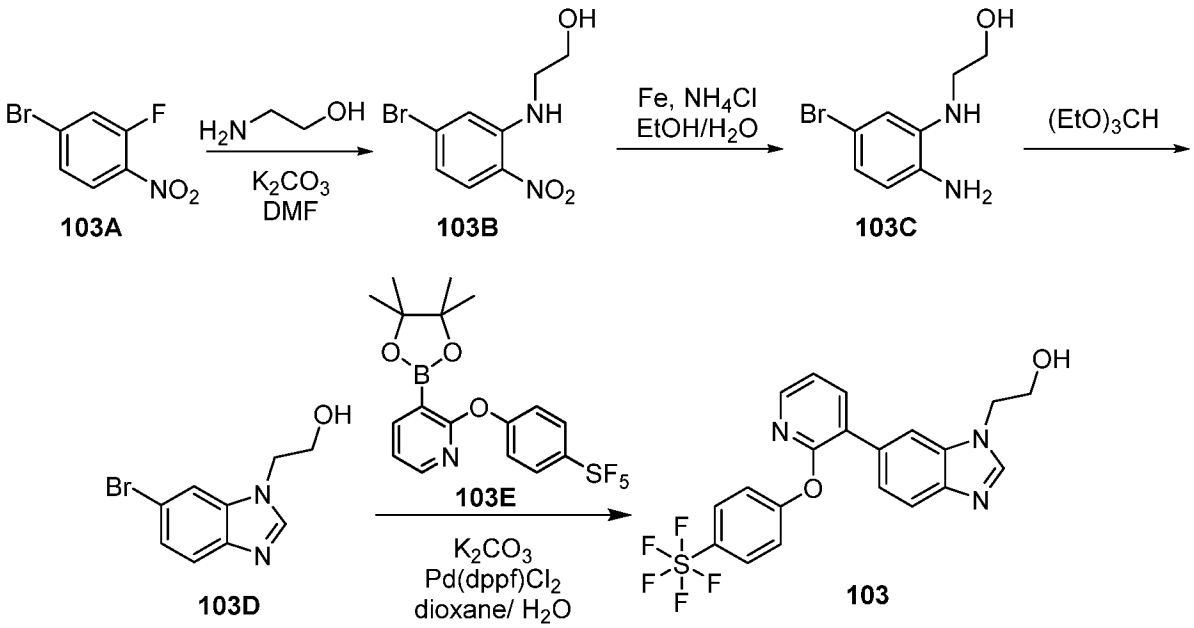
[00377] **Compound 101** was prepared by employing the procedure for **Compound 100** using intermediate **95A** in lieu of **91A**. LC-MS Calcd.: 456.1, m/z found: 456.9.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 6.85 (d, *J*=6.97 Hz, 1 H) 7.68 (d, *J*=8.62 Hz, 2 H) 7.92 (s, 1 H) 7.93 (s, 1 H) 8.02 (d, *J*=8.80 Hz, 1 H) 8.30 (dd, *J*=8.71, 1.74 Hz, 1 H) 8.50 (d, *J*=6.97 Hz, 1 H) 8.58 (d, *J*=2.57 Hz, 1 H) 8.67 (d, *J*=2.57 Hz, 1 H) 8.77 (d, *J*=1.65 Hz, 1 H) 9.10 (br s, 2 H) 13.86 (br s, 1 H).

Example 102: 3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine (Compound 102)



[00378] **Compound 102** was prepared by employing the procedure for **Compound 83** using 2-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-ol (**102A)** in lieu of **76B**. LC-MS Calcd.: 457 ([M+H]+), m/z found: 456.9. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 3.76 - 3.84 (m, 3 H) 4.52 (t, *J*=4.95 Hz, 2 H) 7.03 - 7.15 (m, 1 H) 7.60 (br d, *J*=8.44 Hz, 1 H) 7.66 - 7.72 (m, 5 H) 7.90 (d, *J*=8.44 Hz, 1 H) 8.11 (s, 1 H) 8.30 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.42 (s, 1 H) 9.30 (br s, 1 H).

Example 103: 2-(6-(2-(4-(Pentafluoro- λ^6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-ol (Compound 103)



2-((5-bromo-2-nitrophenyl)amino)ethan-1-ol

[00379] 4-Bromo-2-fluoro-1-nitrobenzene (**103A**, 1 eq) and K_2CO_3 (2 eq.) were dissolved in DMF (0.5M). 2-Aminoethan-1-ol (2 eq) was added slowly. The reaction mixture allowed to continue until LCMS indicated the consumption of starting material. The reaction mixture was diluted with water. The resulting slurry was filtered and the solid was collected and dried to give intermediate **103B** (719 mg, 91%), which was used in the next step without further purification. LC-MS Calcd.: 260 m/z found: 261 ($[M+H]^+$).

2-((2-amino-5-bromophenyl)amino)ethan-1-ol

[00380] Intermediate **103B** and NH_4Cl (10 eq) were dissolved in an ethanol:water mixture (1:1, 0.2M). To this reaction mixture was added Fe (10 eq.). The reaction mixture was heated to reflux and was allowed to continue until LCMS indicated the consumption of starting material. The reaction mixture was filtered through a pad of Celite. The filtrate was diluted with EtOAc, and

washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated to give intermediate **103C**, which was used in the next step without further purification. LC-MS Calcd.: 230 m/z found: 231 ($[M+H]^+$).

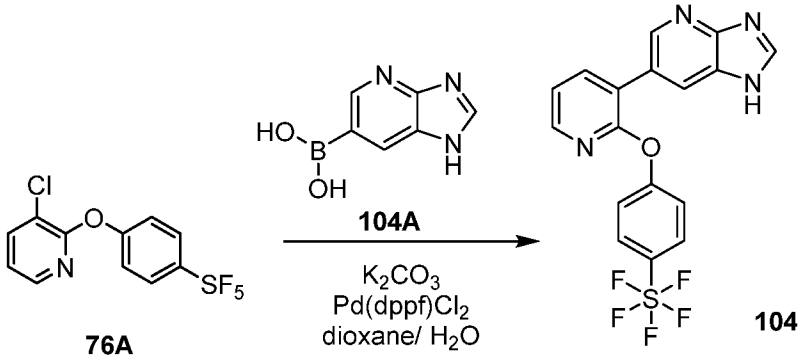
2-(6-bromo-1*H*-benzo[*d*]imidazol-1-yl)ethan-1-ol

[00381] Intermediate **103C** was dissolved in $(EtO)_3CH$ and heated to 100 °C. The reaction mixture was allowed to continue until LCMS indicated the consumption of starting material. The reaction mixture was allowed to cool to temperature and was concentrated and placed on a high vacuum overnight to give intermediate **103D**, which was used in the next step without further purification. LC-MS Calcd.: 240 m/z found: 241 ($[M+H]^+$).

2-(6-(2-(4-(pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-ol

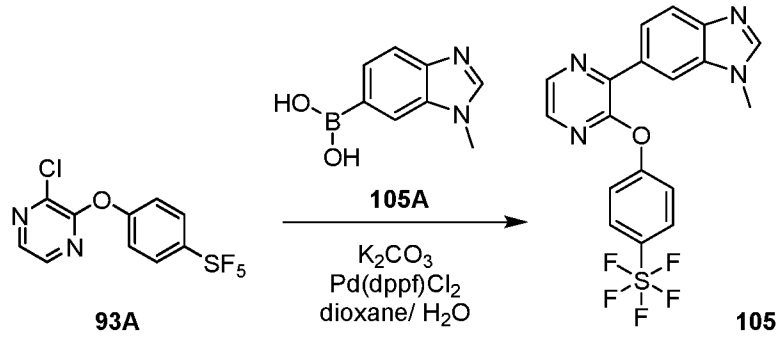
[00382] 2-(4-(pentafluoro- λ⁶-sulfaneyl)phenoxy)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (**103E**, 1 eq) and intermediate **103C** (1.2 eq) were suspended in K_2CO_3 2M/dioxane (0.2M) and thoroughly purged with N_2 over 10 min. To this reaction mixture was added $Pd(dppf)Cl_2$ (0.1 eq.) and the reaction mixture was heated to 80 °C until LCMS indicated the consumption of starting material. The reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with NH_4Cl, H_2O, and brine. The organic layers were dried over Na_2SO_4, concentrated, and purified by flash column chromatography to afford **Compound 103**. LC-MS Calcd.: 458 ([M+H]+), m/z found: 458.0 ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 3.98 - 4.03 (m, 2 H) 4.62 - 4.81 (m, 2 H) 7.27 (d, *J*=8.99 Hz, 2 H) 7.40 (dd, *J*=7.52, 4.95 Hz, 1 H) 7.85 (s, 1 H) 7.86 (s, 1 H) 7.95 (d, *J*=1.10 Hz, 2 H) 8.09 (d, *J*=7.70 Hz, 1 H) 8.26 (d, *J*=5.88 Hz, 1 H) 8.26 (s, 1 H) 9.42 (s, 1 H).

Example 104: 6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1H-imidazo[4,5-b]pyridine (Compound 104)



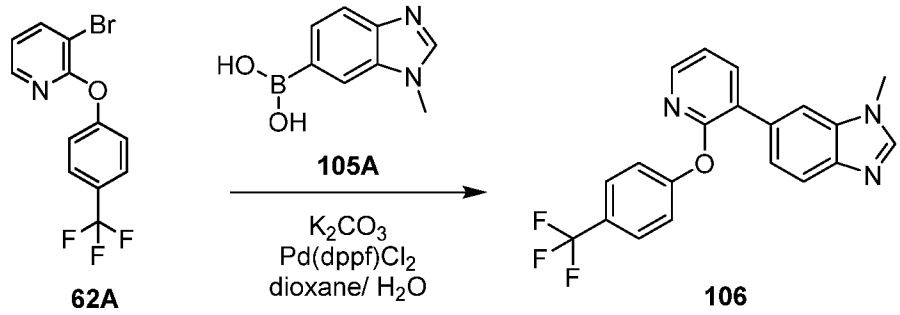
[00383] **Compound 104** was prepared by employing the procedure for **Compound 76** using (1H-imidazo[4,5-b]pyridin-6-yl)boronic acid (**104A**) in lieu of **76B**. LC-MS Calcd.: 415 ([M+H]+), m/z found: 414.9.

Example 105: 1-Methyl-6-(3-(4-(pentafluoro-λ^6-sulfaneyl)phenoxy)pyrazin-2-yl)-1*H*-benzo[*d*]imidazole (Compound 105)



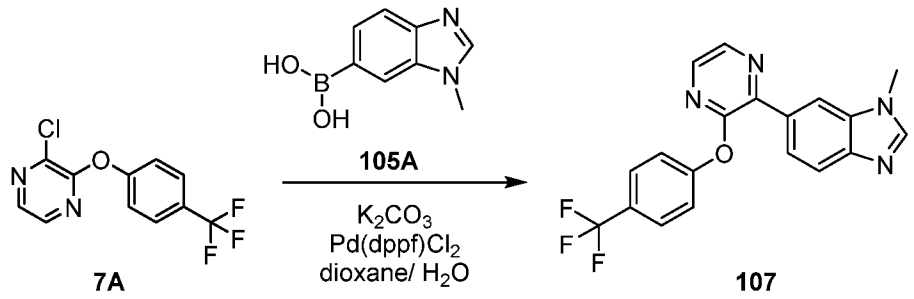
[00384] **Compound 105** was prepared by employing the procedure for **Compound 93** using (1-methyl-1H-benzo[d]imidazol-6-yl)boronic acid (**105A**) in lieu of intermediate **91A**. LC-MS calcd. $C_{18}H_{13}F_5N_4OS$, 428. m/z found, 429 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 1.04 - 1.07 (m, 3 H) 3.49 - 3.53 (m, 1 H) 7.11 (dd, *J*=7.43, 4.86 Hz, 1 H) 7.33 (dd, *J*=8.34, 1.74 Hz, 1 H) 7.67 - 7.76 (m, 7 H) 8.28 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.30 (s, 1 H) 8.40 (s, 1 H).

Example 106: 1-Methyl-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 106)



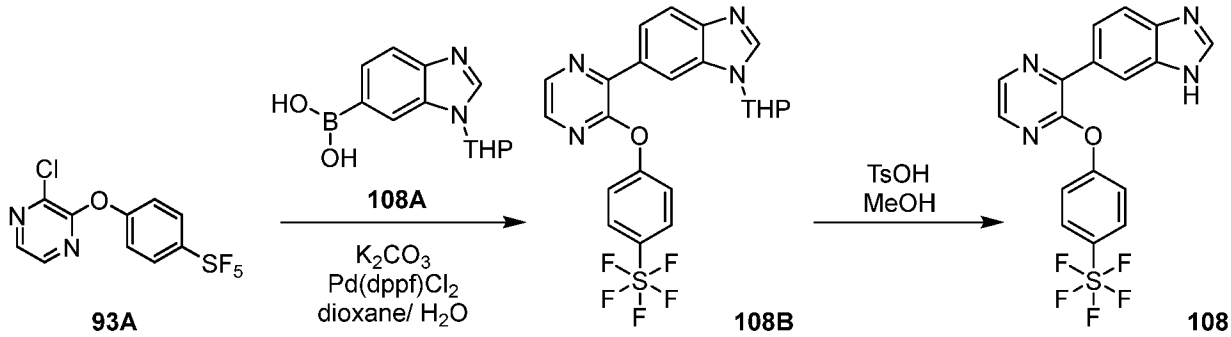
[00385] **Compound 106** was prepared by employing the procedure for **Compound 78** using (1-methyl-1H-benzo[d]imidazol-6-yl)boronic acid (**105A**) in lieu of **76B**. LC-MS mass calcd. $C_{20}H_{14}F_3N_3O$, 369. m/z found, 370 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 4.03 (s, 4 H) 7.55 (d, *J*=8.99 Hz, 2 H) 7.92 (d, *J*=8.62 Hz, 1 H) 8.00 - 8.03 (m, 2 H) 8.19 (dd, *J*=8.62, 1.47 Hz, 1 H) 8.26 (d, *J*=2.38 Hz, 1 H) 8.46 (d, *J*=0.73 Hz, 1 H) 8.61 (d, *J*=2.38 Hz, 1 H) 9.06 (br s, 1 H).

Example 107: 1-Methyl-6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole (Compound 107)



[00386] **Compound 107** was prepared by employing the procedure for **Compound 57** using (1-methyl-1H-benzo[d]imidazol-6-yl)boronic acid (**105A**) in lieu of **46A** (13 mg (35%). LC-MS mass calcd. $C_{19}H_{13}F_3N_4O$, 370. m/z found, 371 $[M+H]^+$. ^1H NMR (600 MHz, DMSO-d_6) δ ppm 4.01 (s, 3 H) 7.53 (d, *J*=8.44 Hz, 2 H) 7.84 (d, *J*=8.44 Hz, 2 H) 7.89 (d, *J*=8.44 Hz, 1 H) 8.16 (dd, *J*=8.53, 1.56 Hz, 1 H) 8.24 (d, *J*=2.57 Hz, 1 H) 8.43 (s, 1 H) 8.60 (d, *J*=2.38 Hz, 1 H) 8.92 (br s, 1 H).

Example 108: 1-Methyl-6-(3-(4-(pentafluoro-λ^6-sulfaneyl)phenoxy)pyrazin-2-yl)-1*H*-benzo[*d*]imidazole (Compound 108)



6-(3-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d]imidazole

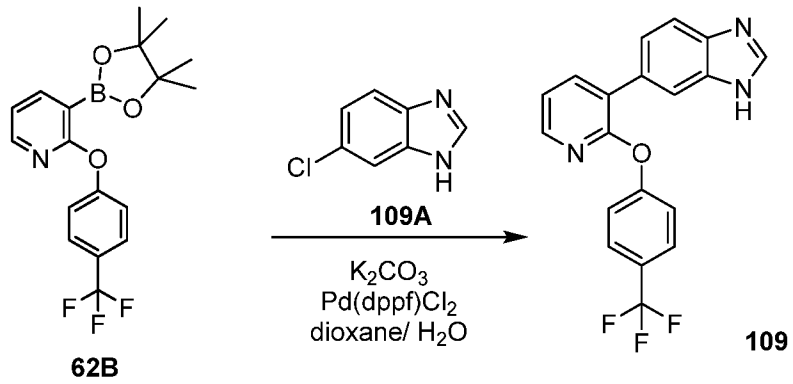
[00387] Intermediate **108B** was prepared by employing the procedure for **Compound 93** using (1-(tetrahydro-2H-pyran-2-yl)-1H-benzo[d]imidazol-6-yl)boronic acid (**108A**) in lieu of intermediate **91A**.

6-(3-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole

[00388] TsOH (3 eq.) was added to a solution of intermediate **108B** (1 eq.) in MeOH/H_2O (5:1, *v*/*v*). The reaction mixture was heated to 80 °C for 2 hr. After completion, solvents were removed under reduced pressure, and purified by HPLC to afford **Compound 108**. LC-MS Calcd.: 415 ([M+H]+), m/z found: 415. ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 7.54 (d, *J*=8.99 Hz, 2 H) 7.91

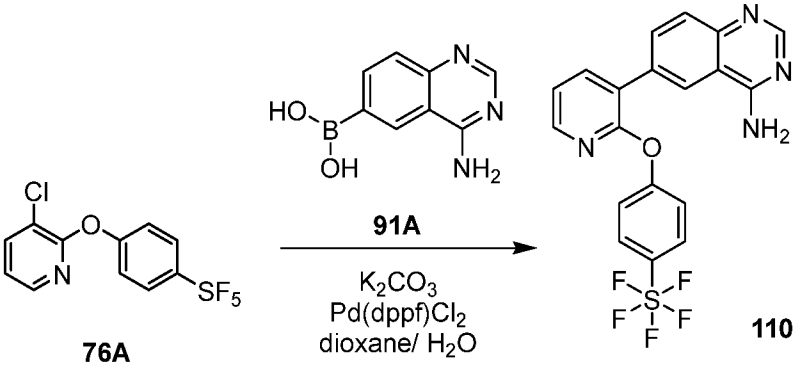
(d, *J*=8.62 Hz, 1 H) 7.99 - 8.05 (m, 2 H) 8.19 (dd, *J*=8.62, 1.65 Hz, 1 H) 8.24 (d, *J*=2.57 Hz, 1 H) 8.48 (d, *J*=0.92 Hz, 1 H) 8.61 (d, *J*=2.38 Hz, 1 H) 9.14 (br s, 1 H).

Example 109: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 109)



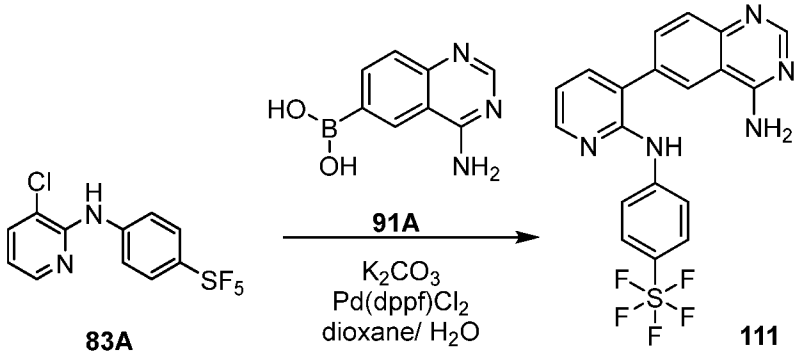
[00389] **Compound 109** was prepared by employing the procedure for **Compound 62** using 6-chloro-1H-benzo[d]imidazole (**109A**) in lieu of **62C**. LC-MS Calcd.: 456 ([M+H]+), m/z found: 456. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.32 - 7.44 (m, 3 H) 7.69 - 7.81 (m, 3 H) 7.87 (d, J=8.44 Hz, 1 H) 8.07 (td, J=7.29, 1.38 Hz, 2 H) 8.21 (dd, J=4.77, 1.83 Hz, 1 H) 9.14 (br s, 1 H).

Example 110: 6-(2-(4-(Pentafluoro- λ^6-sulfaneyl)phenoxy)pyridin-3-yl)quinazolin-4-amine (Compound 110)



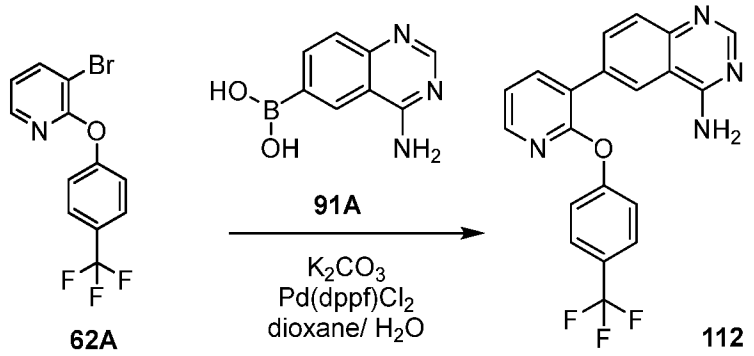
[00390] **Compound 110** was prepared by employing the procedure for **Compound 76** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **76B**. LC-MS Calcd.: 440.1, m/z found: 441.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.36 - 7.45 (m, 3 H) 7.85 (d, *J*=8.80 Hz, 1 H) 7.92 - 7.99 (m, 2 H) 8.11 (dd, *J*=7.52, 1.83 Hz, 1 H) 8.25 (dd, *J*=4.86, 1.93 Hz, 1 H) 8.38 (dd, *J*=8.71, 1.19 Hz, 1 H) 8.70 (d, *J*=1.65 Hz, 1 H) 8.83 (s, 1 H) 9.71 (br s, 2 H).

Example 111: 6-(2-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine (Compound 111)



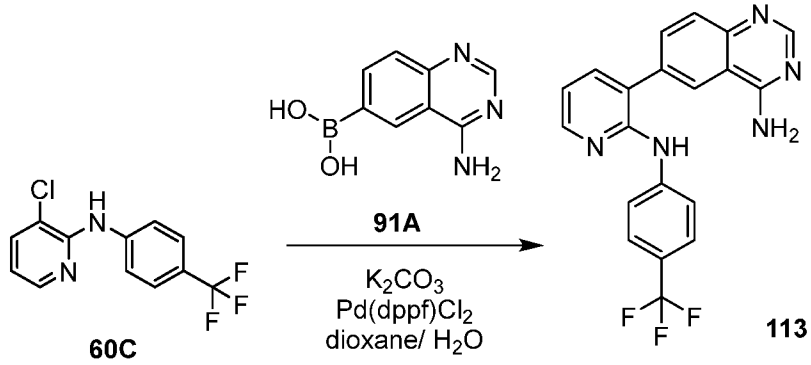
[00391] **Compound 111** was prepared by employing the procedure for **Compound 83** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **76B**. LCMS Calcd.: 440 ([M+H]+), m/z found: 440.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.15 (dd, *J*=7.43, 4.86 Hz, 1 H) 7.65 - 7.74 (m, 5 H) 7.87 (d, *J*=8.62 Hz, 1 H) 8.13 (dd, *J*=8.62, 1.83 Hz, 1 H) 8.33 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.57 (d, *J*=11.16 Hz, 2 H) 8.89 (s, 1 H) 9.79 (s, 1 H) 9.81 (s, 1 H).

Example 112: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinazolin-4-amine (Compound 112)



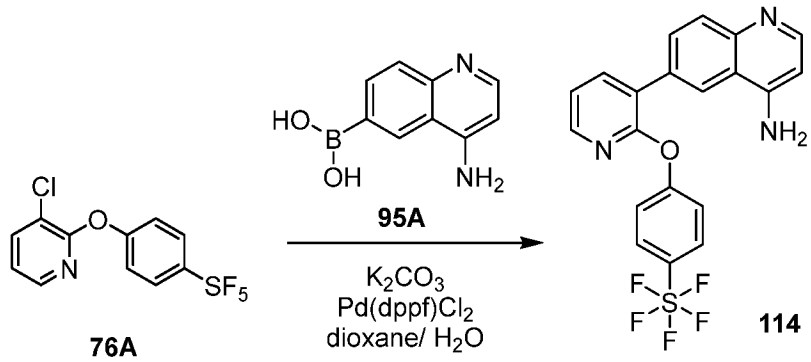
[00392] **Compound 112** was prepared by employing the procedure for **Compound 78** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **76B**. LC-MS Calcd.: 383 ([M+H]+), m/z found: 383.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 7.29 - 7.50 (m, 3 H) 7.80 (d, *J*=8.62 Hz, 2 H) 7.86 (d, *J*=8.80 Hz, 1 H) 8.11 (dd, *J*=7.52, 1.83 Hz, 1 H) 8.26 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.39 (dd, *J*=8.71, 1.74 Hz, 1 H) 8.71 (d, *J*=1.65 Hz, 1 H) 8.83 (s, 1 H) 9.64 (br s, 2 H).

Example 113: 6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine (Compound 113)



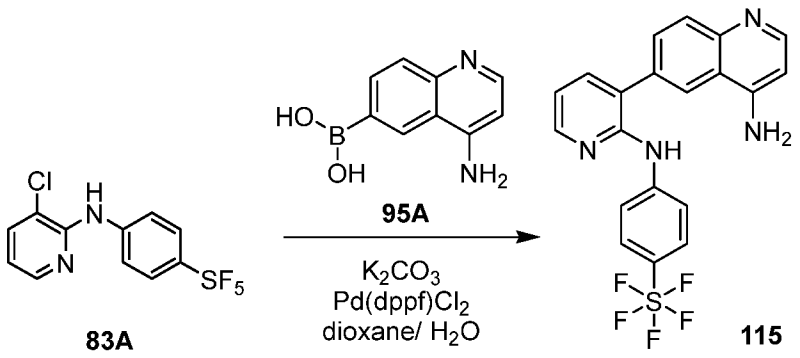
[00393] **Compound 113** was prepared by employing the procedure for **Compound 60** using (4-aminoquinazolin-6-yl)boronic acid (**91A**) in lieu of **46A**. LC-MS Calcd.: 381.1 m/z found: 382.0 ($[M+H]^+$). 1H NMR (600 MHz, DMSO-d6) δ ppm 7.14 (dd, *J*=7.43, 4.86 Hz, 1 H) 7.56 (d, *J*=8.80 Hz, 2 H) 7.70 - 7.75 (m, 3 H) 7.88 (d, *J*=8.62 Hz, 1 H) 8.15 (dd, *J*=8.62, 1.65 Hz, 1 H) 8.34 (dd, *J*=4.95, 1.83 Hz, 1 H) 8.44 (s, 1 H) 8.60 (d, *J*=1.65 Hz, 1 H) 8.90 (s, 1 H) 9.79 (br s, 2 H).

Example 114: 6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4-amine (Compound 114)



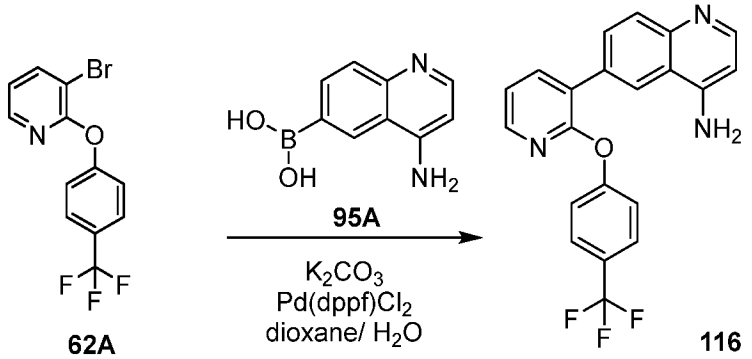
[00394] **Compound 114** was prepared by employing the procedure for **Compound 76** using 4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **76B**. LC-MS Calcd.: 439.1, m/z found: 440.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.67 (d, *J*=5.87 Hz, 1 H) 7.36 - 7.45 (m, 3 H) 7.86 (d, *J*=8.80 Hz, 1 H) 7.94 - 7.98 (m, 2 H) 8.06 (br d, *J*=8.25 Hz, 1 H) 8.12 (dd, *J*=7.43, 1.93 Hz, 1 H) 8.24 (dd, *J*=4.95, 1.83 Hz, 1 H) 8.38 (d, *J*=5.87 Hz, 1 H) 8.53 (s, 1 H).

Example 115: 6-(2-((4-(Pentafluoro- λ⁶-sulfaneyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine (Compound 115)



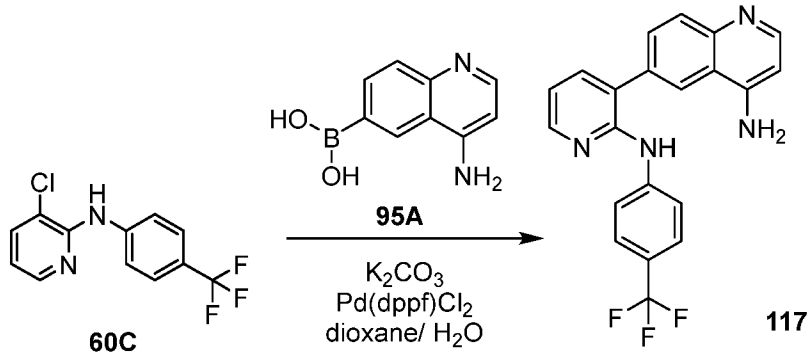
[00395] **Compound 115** was prepared by employing the procedure for **Compound 83** using 4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **76B**. LC-MS Calcd.: 438.1, m/z found: 438.9 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 6.65 (d, *J*=5.69 Hz, 1 H) 7.13 (dd, *J*=7.34, 4.77 Hz, 1 H) 7.68 - 7.75 (m, 5 H) 7.76 (br d, *J*=7.52 Hz, 1 H) 7.86 (d, *J*=8.62 Hz, 1 H) 8.31 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.35 - 8.39 (m, 2 H) 8.48 (s, 1 H).

Example 116: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4-amine (Compound 116)



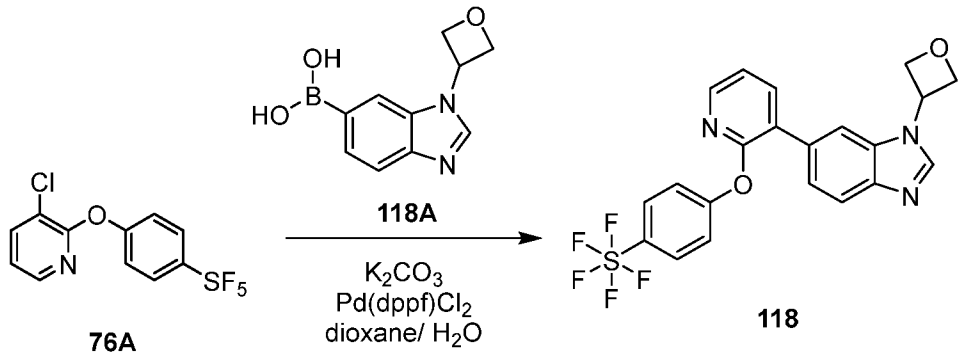
[00396] **Compound 116** was prepared by employing the procedure for **Compound 78** using 4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **76B**. LC-MS Calcd.: 381.1, m/z found: 382.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 6.64 (d, J=5.69 Hz, 1 H) 7.30 - 7.48 (m, 5 H) 7.78 (d, J=8.62 Hz, 2 H) 7.84 (d, J=8.80 Hz, 1 H) 8.02 (dd, J=8.71, 1.56 Hz, 1 H) 8.11 (dd, J=7.43, 1.93 Hz, 1 H) 8.21 (dd, J=4.77, 1.83 Hz, 1 H) 8.36 (d, J=5.50 Hz, 1 H) 8.49 (d, J=1.47 Hz, 2 H).

Example 117: 6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine (Compound 117)



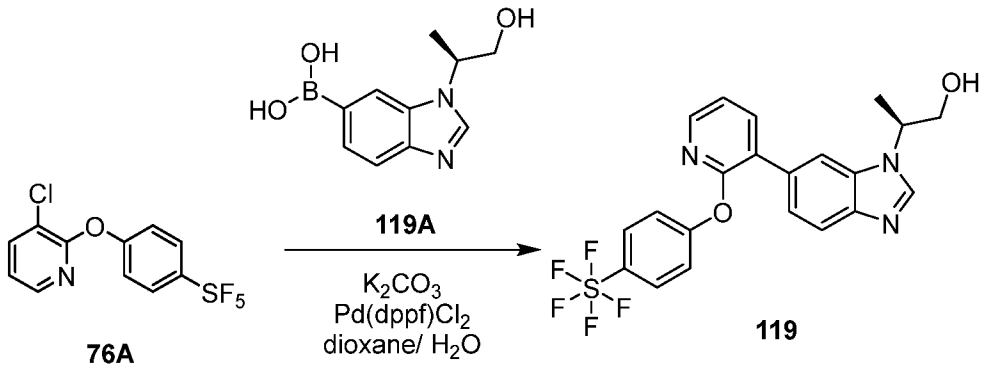
[00397] **Compound 117** was prepared by employing the procedure for **Compound 60** using 4-aminoquinolin-6-yl)boronic acid (**95A**) in lieu of **46A**. LC-MS Calcd.: 380.1 m/z found: 381.0 ($[M+H]^+$). 1H NMR (600 MHz, DMSO-d6) δ ppm 6.70 (d, *J*=6.05 Hz, 1 H) 7.12 (dd, *J*=7.34, 4.95 Hz, 1 H) 7.55 (d, *J*=8.62 Hz, 2 H) 7.71 (dd, *J*=7.43, 1.93 Hz, 1 H) 7.74 (d, *J*=8.62 Hz, 2 H) 7.80 - 7.93 (m, 3 H) 8.31 (dd, *J*=4.95, 1.83 Hz, 1 H) 8.36 (s, 1 H) 8.40 (d, *J*=6.05 Hz, 1 H) 8.43 (s, 1 H).

Example 118: 1-(Oxetan-3-yl)-6-(2-(4-(pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 118)



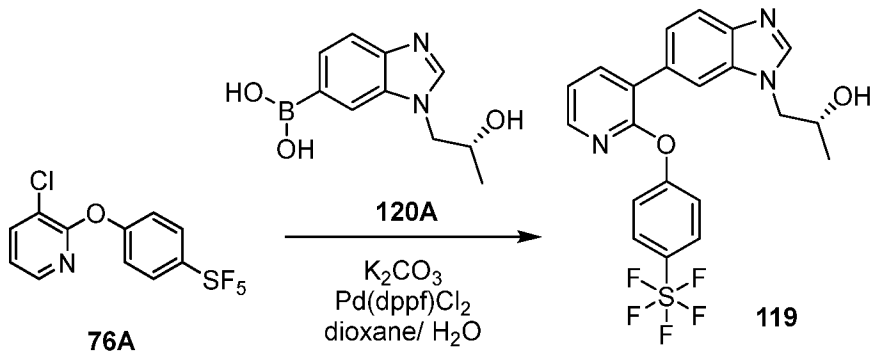
[00398] **Compound 118** was prepared by employing the procedure for **Compound 76** using (1-(oxetan-3-yl)-1H-benzo[d]imidazol-6-yl)boronic acid (**118A**) in lieu of **76B**. LC-MS Calcd.: 470 ([M+H]+), m/z found: 470.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 5.03 (dd, *J*=7.34, 6.05 Hz, 2 H) 5.08 - 5.13 (m, 2 H) 5.84 - 5.90 (m, 1 H) 7.37 (d, *J*=8.99 Hz, 2 H) 7.39 -7.42 (m, 1 H) 7.73 (dd, *J*=8.44, 1.47 Hz, 1 H) 7.88 (d, *J*=8.44 Hz, 1 H) 7.92 - 7.98 (m, 2 H) 8.09 - 8.13 (m, 1 H) 8.21 (d, *J*=0.92 Hz, 1 H) 8.23 (dd, *J*=4.86, 1.93 Hz, 1 H) 9.12 (br s, 1 H).

Example 119: (*S*)-2-(6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1*H*-benzo[*d*]imidazol-1-yl)propan-1-ol (Compound 119)



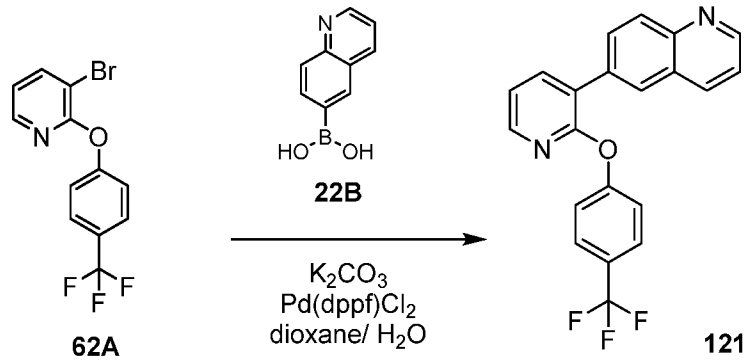
[00399] **Compound 119** was prepared by employing the procedure for **Compound 76** using (S)-(1-(1-hydroxypropan-2-yl)-1H-benzo[d]imidazol-6-yl)boronic acid (**119A**) in lieu of **76B**. LC-MS Calcd.: 472 ([M+H]+), m/z found: 472.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 1.60 (d, *J*=6.79 Hz, 3 H) 3.76 - 3.82 (m, 3 H) 4.90 - 4.98 (m, 1 H) 7.36 - 7.43 (m, 3 H) 7.83 (d, *J*=8.42 Hz, 1 H) 7.91 (d, *J*=8.62 Hz, 1 H) 7.93 - 7.97 (m, 2 H) 8.10 (dd, *J*=7.52, 1.83 Hz, 1 H) 8.24 (dd, *J*=4.77, 1.83 Hz, 1 H) 8.26 (s, 1 H) 9.39 (br s, 1 H).

Example 120: (*S*)-1-(6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[*d*]imidazol-1-yl)propan-2-ol (Compound 120)



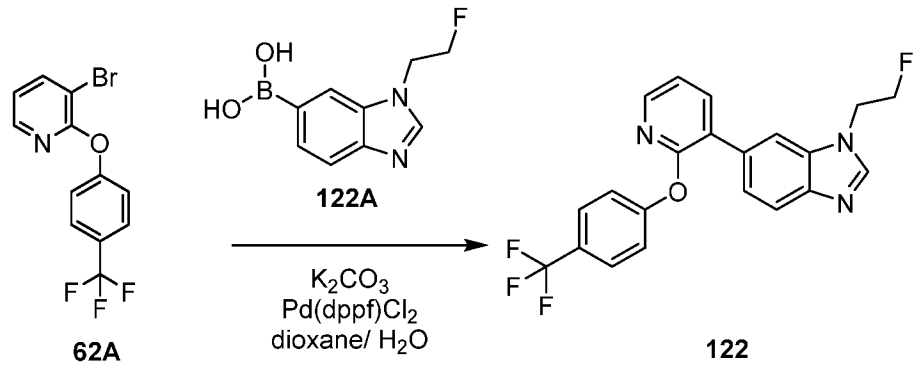
[00400] **Compound 120** was prepared by employing the procedure for **Compound 76** using ((R)-(1-(2-hydroxypropyl)-1H-benzo[d]imidazol-6-yl)boronic acid (**120A**) in lieu of **76B**. LC-MS Calcd.: 472 ([M+H]+), m/z found: 472.0. ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm: 1.16 (d, *J*=6.24 Hz, 3 H) 4.02 - 4.08 (m, 1 H) 4.26 (dd, *J*=14.12, 8.25 Hz, 1 H) 4.51 (dd, *J*=13.94, 3.12 Hz, 1 H) 7.34 - 7.44 (m, 3 H) 7.82 (dd, *J*=8.53, 1.38 Hz, 1 H) 7.90 (d, *J*=8.44 Hz, 1 H) 7.92 - 7.97 (m, 2 H) 8.09 (dd, *J*=7.43, 1.93 Hz, 1 H) 8.25 (s, 2 H) 9.23 (br s, 1 H).

Example 121: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinoline (Compound 121)



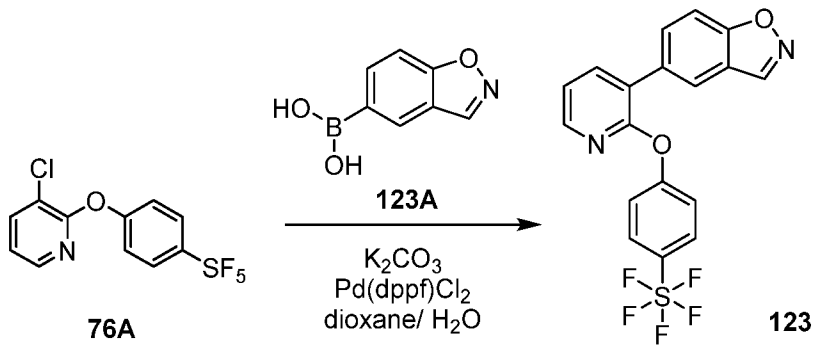
[00401] **Compound 121** was prepared by employing the procedure for **Compound 78** using quinolin-6-ylboronic acid (**95A**) in lieu of **76B**. LC-MS Calcd.: 366.1 m/z found: 367.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.23 - 7.28 (m, 3 H) 7.47 (dd, *J*=8.25, 4.22 Hz, 1 H) 7.63 (d, *J*=8.62 Hz, 2 H) 7.97 (d, *J*=1.28 Hz, 2 H) 8.00 (dd, *J*=7.52, 1.83 Hz, 1 H) 8.08 (dd, *J*=4.86, 1.93 Hz, 1 H) 8.15 (s, 1 H) 8.33 (dd, *J*=8.25, 1.47 Hz, 1 H) 8.82 (dd, *J*=4.22, 1.65 Hz, 1 H).

Example 122: 1-(2-Fluoroethyl)-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole (Compound 122)



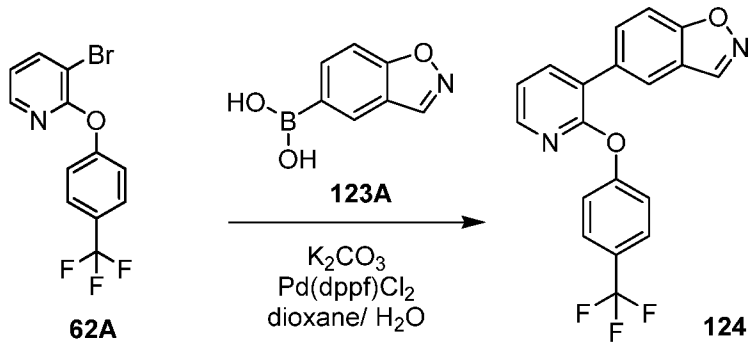
[00402] **Compound 122** was prepared by employing the procedure for **Compound 78** using (1-(2-fluoroethyl)-1H-benzo[d]imidazol-6-yl)boronic acid (**122A**) in lieu of **76B**. LC-MS Calcd.: 402 ([M+H]+), m/z found: 402.1. ^1H NMR (600 MHz, DMSO-*d*6) δ ppm: 4.71 - 4.76 (m, 1 H) 4.76 - 4.83 (m, 2 H) 4.88 - 4.93 (m, 1 H) 7.35 - 7.40 (m, 3 H) 7.72 (dd, *J*=8.50, 1.50 Hz, 1 H) 7.78 (d, *J*=8.50 Hz, 2 H) 7.84 (d, *J*=8.38 Hz, 1 H) 8.07 (dd, *J*=7.50, 1.88 Hz, 1 H) 8.12 (s, 1 H) 8.21 (dd, *J*=4.88, 1.88 Hz, 1 H) 8.87 (s, 1 H).

Example 123: 5-(2-(4-(Pentafluoro-λ^6-sulfaneyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole (Compound 123)



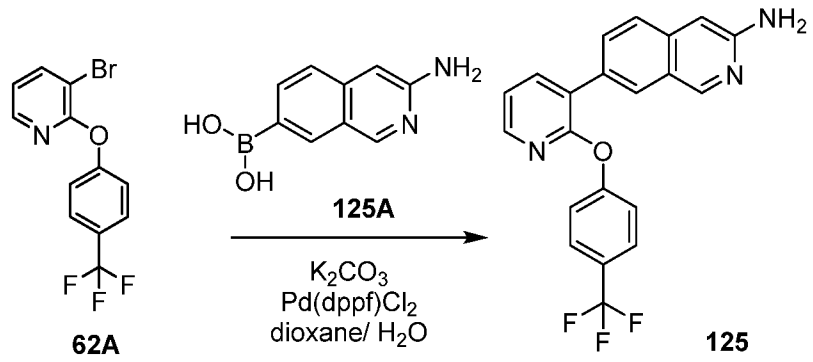
[00403] **Compound 123** was prepared by employing the procedure for **Compound 76** using benzo[d]isoxazol-5-ylboronic acid (**123A**) in lieu of **76B** (10 mg, 40%). LC-MS mass calcd. $C_{18}H_{11}F_5N_2O_2S$, 414. m/z found, 415 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 7.10 (d, *J*=8.78 Hz, 1 H) 7.32 (dd, *J*=7.40, 4.89 Hz, 1 H) 7.38 (d, *J*=8.78 Hz, 2 H) 7.79 - 7.86 (m, 1 H) 7.91 7.97 (m, 3 H) 8.00 (dd, *J*=7.53, 1.76 Hz, 1 H) 8.15 (dd, *J*=4.77, 1.76 Hz, 1 H).

Example 124: 5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole (Compound 124)



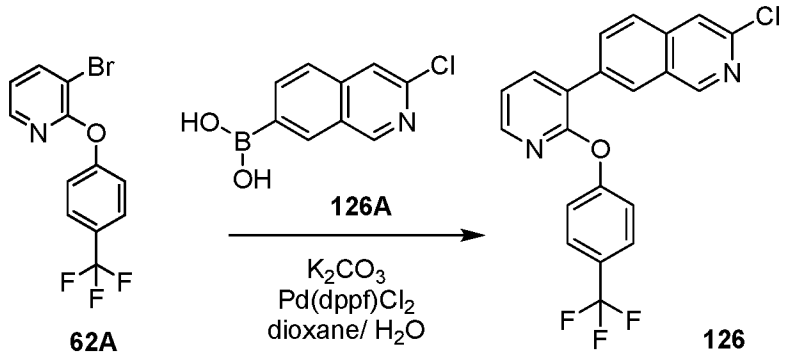
[00404] **Compound 124** was prepared by employing the procedure for **Compound 78** using benzo[d]isoxazol-5-ylboronic acid (**123A**) in lieu of **76B**. LC-MS Calcd.: 357 ([M+H]+), m/z found: 357. ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 7.12 (d, J=8.53 Hz, 1 H) 7.30 (dd, J=7.40, 4.89 Hz, 1 H) 7.38 (d, J=8.28 Hz, 2 H) 7.78 (d, J=8.53 Hz, 2 H) 7.84 (dd, J=8.66, 2.38 Hz, 1 H) 7.93 (d, J=2.26 Hz, 1 H) 7.99 (dd, J=7.53, 1.76 Hz, 1 H) 8.14 (dd, J=4.77, 1.76 Hz, 1 H).

Example 125: 7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-3-amine (Compound 125)



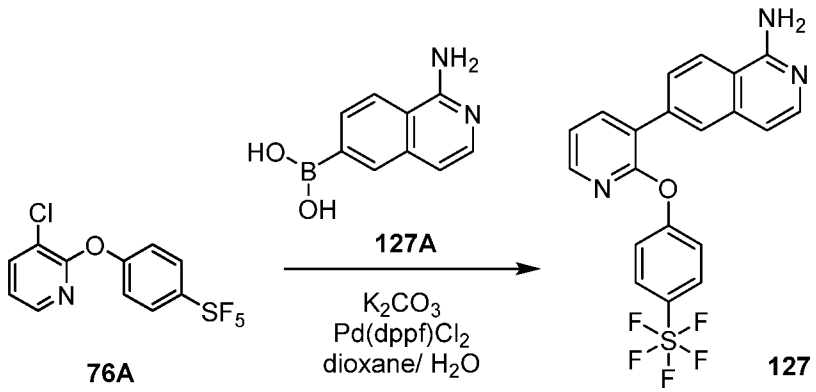
[00405] **Compound 125** was prepared by employing the procedure for **Compound 78** using (3-aminoisoquinolin-7-yl)boronic acid (**125A**) in lieu of **76B**. LC-MS Calcd.: 381.1 m/z found: 382.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 6.90 (s, 1 H) 7.34 - 7.43 (m, 3 H) 7.72 (d, *J*=8.78 Hz, 1 H) 7.78 (d, *J*=8.53 Hz, 2 H) 7.90 (dd, *J*=8.78, 1.76 Hz, 1 H) 8.09 (dd, *J*=7.53, 1.76 Hz, 1 H) 8.17 - 8.22 (m, 2 H) 9.02 (s, 1 H).

Example 126: 3-Chloro-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 126)



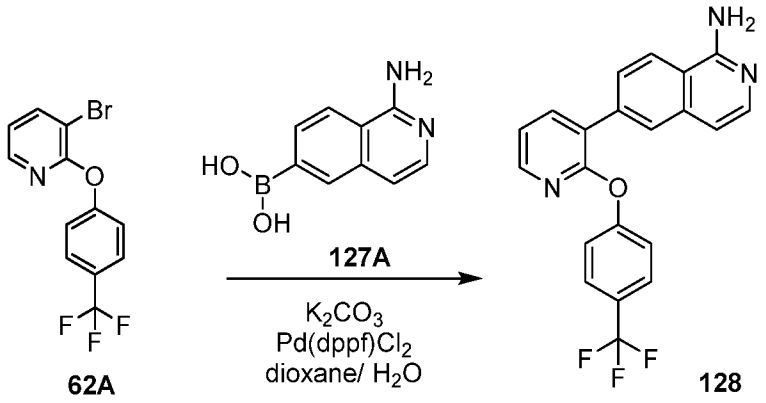
[00406] **Compound 126** was prepared by employing the procedure for **Compound 78** using (3-chloroisoquinolin-7-yl)boronic acid (**126A**) in lieu of **76B**. LCMS Calcd.: 400.1 m/z found: 401.0 ($[M+H]^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.38 - 7.47 (m, 3 H) 7.79 (d, *J*=8.53 Hz, 2 H) 8.05 - 8.13 (m, 2 H) 8.17 (ddd, *J*=12.11, 8.09, 1.63 Hz, 2 H) 8.24 (dd, *J*=4.77, 1.76 Hz, 1 H) 8.49 (s, 1 H) 9.29 (s, 1 H).

Example 127: 6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine (Compound 127)



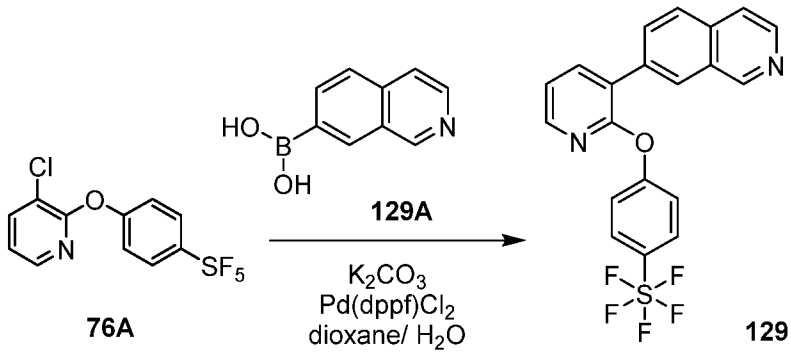
[00407] **Compound 127** was prepared by employing the procedure for **Compound 76** using (1-aminoisoquinolin-6-yl)boronic acid (**127A**) in lieu of **76B**. LC-MS mass Calcd.: 439.1, m/z found: 440.1 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.30 (d, *J*=6.88 Hz, 1 H) 7.40 - 7.47 (m, 3 H) 7.71 (d, *J*=7.00 Hz, 1 H) 7.98 (d, *J*=8.19 Hz, 2 H) 8.12 (dd, *J*=8.76, 1.63 Hz, 1 H) 8.18 (dd, *J*=7.50, 1.88 Hz, 1 H) 8.29 (d, *J*=4.32 Hz, 1 H) 8.28 (s, 1 H) 8.62 (d, *J*=8.63 Hz, 1 H).

Example 128: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine (Compound 128)



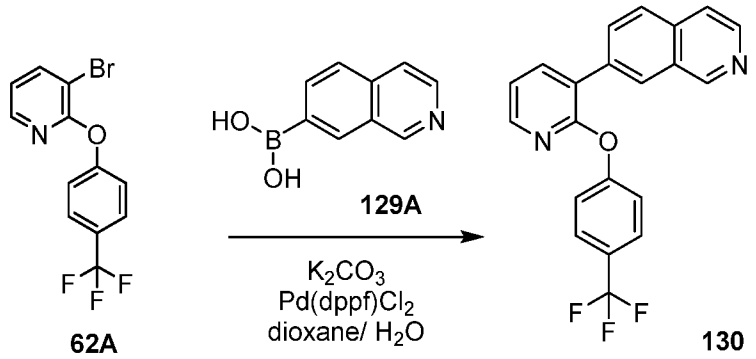
[00408] **Compound 128** was prepared by employing the procedure for **Compound 78** using (1-aminoisoquinolin-6-yl)boronic acid (**127A**) in lieu of **76B**. LCMS Calcd.: 381.1 m/z found: 382.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d*6) δ ppm 7.29 (d, *J*=6.88 Hz, 1 H) 7.40 - 7.45 (m, 3 H) 7.72 (d, *J*=7.00 Hz, 1 H) 7.80 (d, *J*=8.50 Hz, 2 H) 8.12 (dd, *J*=8.69, 1.69 Hz, 1 H) 8.17 (dd, *J*=7.50, 1.88 Hz, 1 H) 8.27 (d, *J*=5.81 Hz, 1 H) 8.28 (s, 1 H) 8.62 (d, *J*=8.76 Hz, 1 H) 9.01 (br s, 2 H).

Example 129: 7-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 129)



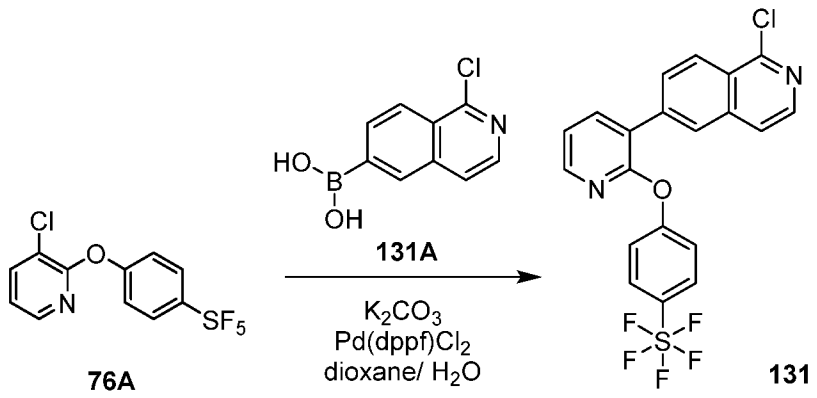
[00409] **Compound 129** was prepared by employing the procedure for **Compound 76** using isoquinolin-7-ylboronic acid (**129A**) in lieu of **76B**. LCMS Calcd.: 424.1, m/z found: 425.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.37 - 7.47 (m, 3 H) 7.89 (d, *J*=5.75 Hz, 1 H) 7.92 - 8.00 (m, 2 H) 8.05 - 8.10 (m, 1 H) 8.10 - 8.14 (m, 1 H) 8.17 (dd, *J*=7.50, 1.88 Hz, 1 H) 8.25 (dd, *J*=4.88, 1.88 Hz, 1 H) 8.43 (s, 1 H) 8.56 (d, *J*=5.75 Hz, 1 H) 9.40 (s, 1 H).

Example 130: 7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 130)



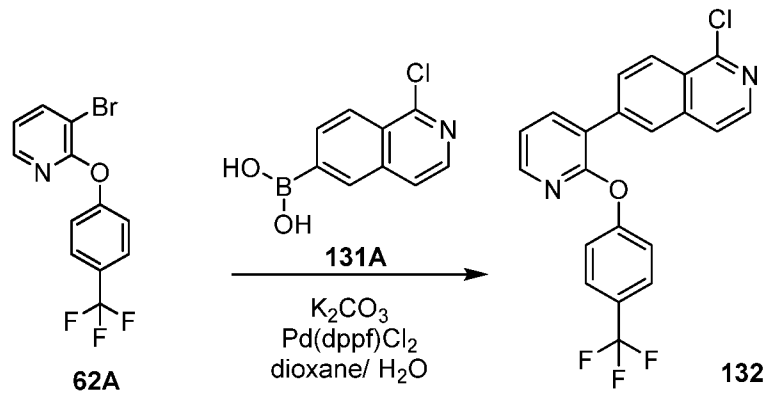
[00410] **Compound 130** was prepared by employing the procedure for **Compound 78** using isoquinolin-7-ylboronic acid (**129A**) in lieu of **76B**. LC-MS Calcd.: 366.1 m/z found: 367.0 ([M+H]$^+$).

Example 131: 1-Chloro-6-(2-(4-(pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 131)



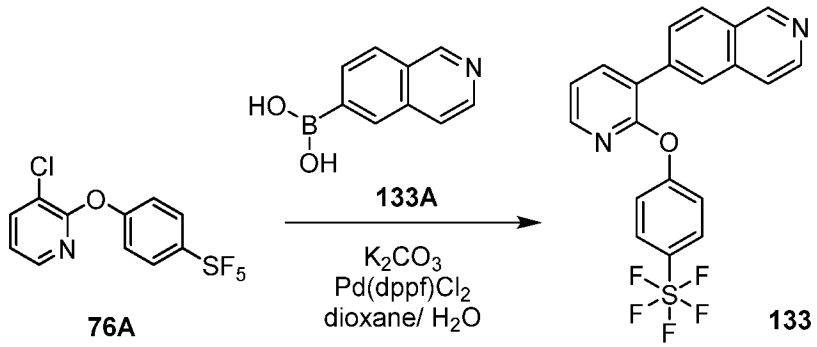
[00411] **Compound 131** was prepared by employing the procedure for **Compound 76** using (1-chloroisoquinolin-6-yl)boronic acid (**131A**) in lieu of **76B**. LC-MS mass Calcd.: 458.0, m/z found: 459.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 7.40 - 7.47 (m, 3 H) 7.94 - 8.01 (m, 3 H) 8.18 (ddd, *J*=11.17, 8.16, 1.76 Hz, 2 H) 8.28 (dd, *J*=4.77, 1.76 Hz, 1 H) 8.34 - 8.41 (m, 3 H).

Example 132: 1-Chloro-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 132)



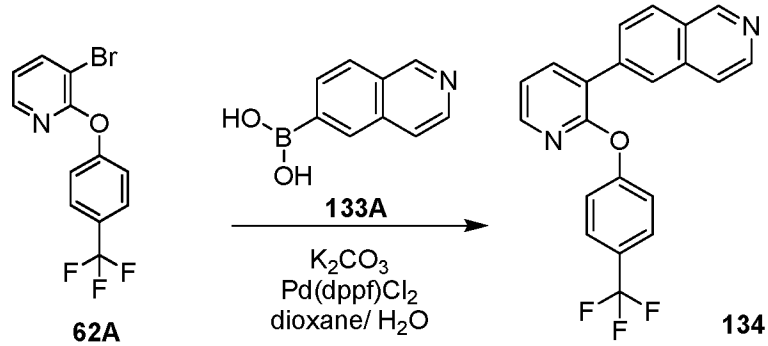
[00412] **Compound 132** was prepared by employing the procedure for **Compound 78** using using (1-chloroisoquinolin-6-yl)boronic acid (**131A**) in lieu of **76B**. LCMS Calcd.: 400.1 m/z found: 401.0 ($[M+H]^+$). ^1H NMR (600 MHz, DMSO-*d6*) δ ppm 7.36 - 7.48 (m, 3 H) 7.79 (d, *J*=8.53 Hz, 2 H) 7.98 (d, *J*=5.52 Hz, 1 H) 8.14 - 8.21 (m, 2 H) 8.26 (dd, *J*=4.77, 1.76 Hz, 1 H) 8.31 - 8.43 (m, 3 H).

Example 133: 6-(2-(4-(Pentafluoro- λ⁶-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 133)



[00413] **Compound 133** was prepared by employing the procedure for **Compound 76** using isoquinolin-6-ylboronic acid (**133A**) in lieu of **76B**. LC-MS mass Calcd.: 424.1, m/z found: 425.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.38 - 7.45 (m, 3 H) 7.90 (d, *J*=5.77 Hz, 1 H) 7.93 - 7.99 (m, 2 H) 8.01 (dd, *J*=8.53, 1.51 Hz, 1 H) 8.16 (dd, *J*=7.53, 2.01 Hz, 1 H) 8.22 (d, *J*=8.53 Hz, 1 H) 8.24 - 8.28 (m, 2 H) 8.56 (d, *J*=5.77 Hz, 1 H) 9.37 (s, 1 H).

Example 134: 6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline (Compound 134)



[00414] **Compound 134** was prepared by employing the procedure for **Compound 78** using using isoquinolin-6-ylboronic acid (**133A**) in lieu of **76B**. LCMS Calcd.: 366.1 m/z found: 367.0 ([M+H]$^+$). ^{1}H NMR (600 MHz, DMSO-*d*6) δ ppm 7.38 - 7.44 (m, 3 H) 7.78 (d, *J*=8.53 Hz, 2 H) 7.90 (d, *J*=5.77 Hz, 1 H) 8.02 (dd, *J*=8.53, 1.51 Hz, 1 H) 8.15 (dd, *J*=7.40, 1.88 Hz, 1 H) 8.22 (d, *J*=8.53 Hz, 1 H) 8.25 (dt, *J*=4.83, 2.48 Hz, 2 H) 8.53 - 8.58 (m, 1 H) 9.34 - 9.39 (m, 1 H).

II. Biological Evaluation

Example A1: YAP Reporter Assay

[00415] HEK293T cells stably transfected with 8XTBD luciferase reporter and pRLTK in 384-well plates were treated with the test compounds, starting from 3 μM (final concentration in assay plate), 1:3 dilution, and 10 points in quadruplicates. Post 24-hr incubation with compounds at 37 °C and 5% CO_2, cells were lysed and 8XTBD-driven firefly luciferase and control TK-driven renilla luciferase activities were measured using Promega Dual-Luciferase Reporter Assay System.

[00416] Reagents: The reagents used for this study were: DMEM: Invitrogen# 11960077, Dual-Glo Luciferase Assay System: Promega-E2980, Puromycin Dihydrochloride: Invitrogen-A1113803, 384-well plate: PerkinElmer-6007480, L-GLUTAMINE: Invitrogen-25030164, Hygromycin B: Invitrogen-10687010 , and Penicillin-Streptomycin: Merk-TMS-AB2-C.

[00417] Media: The media used for this assay were: Culture Medium: DMEM+ 1ug/mL puromycin + 200 ug/mL hygromycin (with 10% FBS + 1mM L-glutamine); and Assay Medium: DMEM (with 10% FBS + 1mM L-glutamine + 1x P/S).

[00418] Cell Plating: The appropriate media was warmed at 37 °C by water bath: Culture Medium, Assay Medium, 1x D-PBS, 0.05% trypsin-EDTA. The cells were trypsinized after removing all media, then washed with 1x sterile D-PBS and then with 2 ml 0.05% trypsin-EDTA. The cells were then incubated at RT for one minute. Then 10 mL/75 cm^2 flask Assay Medium was added to each flask. Using a 10 mL pipette, the cells were then gently resuspended in the media, until the clumps completely disappeared. The cells were then transferred into 50 mL centrifuge tubes and were centrifuged at 800 rpm for 5 mins. The medium was removed, and the cells were resuspended with Assay Medium. An aliquot of cells was used to count the cell density (cells/mL). The cell suspension was then diluted with Assay Medium to a concentration of $6x10^4$ cells/mL. 50 μL cells suspension was then plated to 384-well plate (PerkinElmer-6007480), $3x10^3$ cells/well and the cells were incubated in an incubator at 37 °C, 5% CO_2.

[00419] Compound Treatment: In the afternoon (incubation of the plate with 3-4 hrs), the test compounds were added by Echo, starting from 3 μM (final concentration in the assay plate), 1:3 dilution, 10 points, quadruplicates. The plate was placed at 37°C, 5% CO2 incubator for 24hrs.

[00420] Detection: The Dual-Glo Luciferase Reagent was prepared by transferring the contents of one bottle of Dual-Glo Luciferase Buffer to one bottle of Dual-Glo Luciferase Substrate to create the Dual-Glo Luciferase Reagent. Mixing was performed by inversion until the substrate was thoroughly dissolved. After mixing, the reagent was aliquoted into 15 mL tubes. In the

afternoon (24 hrs post-compound treatment), the DMEM+ medium in the 384 well plates were aspirated by Microplate Washer.

[00421] Measuring firefly luciferase activity: 20 µL Dual-Glo Luciferase Reagent was added to the 384-well plates. The plates were protected from light to prevent interference with the assay. The plates were shaken for 1 min followed centrifuging plates at 1000 rpm for 30 seconds. After waiting at least 10 minutes, the firefly luminescence was measured by Envision.

[00422] Measuring renilla luciferase activity: 20 µL Stop-Glo Reagent was added to the 384-well plates. The plates were shaken for 1 min and then centrifuged at 1000rpm for 30 seconds. After waiting at least 10 minutes, the renilla luminescence was measured by Envision.

[00423] Compounds' IC_{50} and maximum inhibition on the firefly luciferase and renilla luciferase activities were reported separately. IC_{50}'s for firefly luciferase activity of the tested compounds are shown in Table 2.

TABLE 2

Compound #	**Name**	Firefly Luciferase IC_{50} (µM)
1	7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one	A
2	1-methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one	A
3	3-fluoro-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)quinolin-4(1H)-one	A
4	2,4-dichloro-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinazoline	B
5	1-(2-hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one	A
6	3-(1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	A
7	5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole	A
8	5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole	A
9	3-(7-fluoro-1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	A
10	7-fluoro-5-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole	A
11	7-fluoro-5-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-1H-benzo[d][1,2,3]triazole	A

12	6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine	A
13	6-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine	A
14	1-(2,3-dihydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one	A
15	3-(fluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine	A
15A	(7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol	N.D.
16	3-(difluoromethyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-[1,2,4]triazolo[4,3-a]pyridine	A
17	7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide	A
18	4-methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-4H-benzo[e][1,2,4]thiadiazine 1,1-dioxide	A
19	3-(1H-benzo[d]imidazol-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine	A
20	1-methyl-6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	A
20a	1-methyl-5-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	N.D.
21	3-(1-methyl-1H-benzo[d]imidazol-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine	A
21a	3-(1-methyl-1H-benzo[d]imidazol-5-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine	N.D.
22	6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinoline	B
23	N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)-3-(quinolin-6-yl)pyridin-2-amine	C
24	6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinazoline	C
25	6-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)cinnoline	A
26	3-(cinnolin-6-yl)-N-(4-(pentafluoro-λ6-sulfaneyl)phenyl)pyridin-2-amine	C
27	7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-ol	A
28	4-chloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline	A

29	3-(4-chloroquinazolin-7-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	C
30	2,4-dichloro-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinazoline	A
31	3-(2,4-dichloroquinazolin-7-yl)-N-(4-(trifluoromethyl)phenyl)pyrazin-2-amine	B
32	2-methyl-8-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide	A
33	2-methyl-8-(2-((4-(trifluoromethyl)phenyl)thio)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide	A
34	2-methyl-8-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide	D
35	2-methyl-8-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide	D
36	2-methyl-8-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3,4-dihydro-2H-benzo[b][1,4,5]oxathiazepine 1,1-dioxide	C
37	(7-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)methanol	A
38	2-(7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-[1,2,4]triazolo[4,3-a]pyridin-3-yl)propan-2-ol	A
39	7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	C
40	2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	A
41	2-(2-Aminoethyl)-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one	C
42	2-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one	D
43	2-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2*H*)-one	C
44	2-Methyl-6-(2-((4-(trifluoromethyl)phenyl)amino)phenyl)benzo[d]isoxazol-3(2*H*)-one	C
45	7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-[1,2,4]triazolo[4,3-*c*]pyrimidin-3(2*H*)-one	C
46	7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one	A
47	7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one	A
48	1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one	A

49	1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)quinolin-4(1H)-one	A
50	7-(2-((4-(Trifluoromethyl)phenyl)amino)phenyl)-1,6-naphthyridin-4(1*H*)-one	A
51	7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)-1,6-naphthyridin-4(1*H*)-one	A
52	7-(2-(4-(Trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one	A
53	7-(2-((4-(Trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one	A
54	1-Methyl-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)-1,8-naphthyridin-4(1H)-one	A
55	1-Methyl-7-(2-((4-(trifluoromethyl)phenyl)thio)phenyl)-1,8-naphthyridin-4(1H)-one	A
56	7-(3-(4-(Trifluoromethyl)phenoxy)pyridin-2-yl)quinolin-4(1H)-one	A
57	7-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one	A
58	7-(2-((4-(Trifluoromethyl)phenyl)thio)pyridin-3-yl)quinolin-4(1H)-one	A
59	7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one	A
60	7-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4(1H)-one	A
61	7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one	A
62	7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one	A
63	7-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one	A
64	1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4(1H)-one	A
65	1-Methyl-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one	A
66	1-Methyl-7-(3-((4-(trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4(1H)-one	A
67	7-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)-1,6-naphthyridin-4(1H)-one	A
68	*N*,*N*-Dimethyl-2-(4-oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)acetamide	A

69	1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one	A
70	1-(3-Aminopropyl)-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-4(1H)-one	A
71	3-(4-Oxo-7-(2-(4-(trifluoromethyl)phenoxy)phenyl)quinolin-1(4H)-yl)propanamide	A
72	1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one	A
73	1-(3-Hydroxypropyl)-7-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4(1H)-one	A
74	1-(2-Hydroxyethyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one	A
75	1-(3-Hydroxypropyl)-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one	A
76	5-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole	A
77	3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine	A
78	5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole	A
79	3-(7-Fluoro-1H-benzo[d][1,2,3]triazol-5-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine	A
80	7-Fluoro-5-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole	A
81	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine	A
82	7-Fluoro-5-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d][1,2,3]triazole	A
83	3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine	A
84	6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine	A
85	3-(3H-[1,2,3]Triazolo[4,5-b]pyridin-6-yl)-N-(4-(trifluoromethyl)phenyl)pyridin-2-amine	A
86	6-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-3H-[1,2,3]triazolo[4,5-b]pyridine	A
87	1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one	A
88	7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one	A

89	1-(3-Hydroxypropyl)-7-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4(1H)-one	A
90	7-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1,8-naphthyridin-4(1H)-one	A
91	6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine	C
92	6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine	B
93	6-(3-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyrazin-2-yl)quinazolin-4-amine	B
94	6-(3-((4-(pentafluoro- λ6-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinazolin-4-amine	C
95	6-(3-((4-(Trifluoromethyl)phenyl)thio)pyrazin-2-yl)quinolin-4-amine	A
96	6-(3-(4-(Trifluoromethyl)phenoxy)pyrazin-2-yl)quinolin-4-amine	B
97	6-(3-((4-(Trifluoromethyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine	C
98	6-(3-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyrazin-2-yl)quinolin-4-amine	B
99	6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyrazin-2-yl)quinolin-4-amine	B
100	6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinazolin-4-amine	B
101	6-(3-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)thio)pyrazin-2-yl)quinolin-4-amine	B
102	3-(1H-Benzo[d][1,2,3]triazol-5-yl)-N-(4-(pentafluoro- λ6-sulfaneyl)phenyl)pyridin-2-amine	A
103	2-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)ethan-1-ol	A
104	6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-imidazo[4,5-b]pyridine	A
105	1-Methyl-6-(3-(4-(pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole	A
106	1-Methyl-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	A
107	1-Methyl-6-(3-(4-(trifluoromethyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole	A
108	6-(3-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyrazin-2-yl)-1H-benzo[d]imidazole	A

109	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	A
110	6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinazolin-4-amine	B
111	6-(2-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine	A
112	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinazolin-4-amine	A
113	6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinazolin-4-amine	C
114	6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)quinolin-4-amine	C
115	6-(2-((4-(Pentafluoro- λ6-sulfaneyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine	B
116	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinolin-4-amine	B
117	6-(2-((4-(Trifluoromethyl)phenyl)amino)pyridin-3-yl)quinolin-4-amine	A
118	1-(Oxetan-3-yl)-6-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	A
119	(S)-2-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propan-1-ol	A
120	(S)-1-(6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazol-1-yl)propan-2-ol	A
121	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)quinoline	B
122	1-(2-Fluoroethyl)-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)-1H-benzo[d]imidazole	A
123	5-(2-(4-(Pentafluoro-λ6-sulfaneyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole	A
124	5-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)benzo[d]isoxazole	A
125	7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-3-amine	C
126	3-Chloro-7-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline	C
127	6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine	C
128	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinolin-1-amine	C
129	7-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline	C

130	7-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline	C
131	1-Chloro-6-(2-(4-(pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline	C
132	1-Chloro-6-(2-(4-(trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline	B
133	6-(2-(4-(Pentafluoro- λ6-sulfaneyl)phenoxy)pyridin-3-yl)isoquinoline	C
134	6-(2-(4-(Trifluoromethyl)phenoxy)pyridin-3-yl)isoquinoline	C

Note: Biochemical assay IC_{50} data are designated within the following ranges:

A: ≤ 0.1 μM C: > 0.2 μM to ≤ 1.0 μM

B: > 0.1 μM to ≤ 0.2 μM D: > 1.0 μM ≤ 10 μM

N.D.: Not determined

Example A2: Tumor Suppression Assay

[00424] The procedures described herein for the tumor suppression assay is as described in PCT/US2013/043752 (WO 2013/188138). Mouse procedures are performed according to the guidelines of approved animal protocol and based on the methods. After the cells are grown to 90%> confluence, these cells are harvested by trypsinization, washed in phosphate-buffered saline (PBS), and resuspended in PBS supplemented with 50% Matrigel (BD Biosciences). An appropriate amount of cells is prepared for administration, such as 200 μL per injection site. Immuno-compromised mice are injected on the dorsolateral sites subcutaneously. Any one of the compounds described herein is formulated accordingly and is then administered at a suitable dose. Control mice received vehicle alone. The average tumor diameter (two perpendicular axes of the tumor are measured) are recorded. The data are expressed in tumor volume estimated by ([width]2 x length/2). Paired, two-tailed Student's t-test is performed to access the statistical significance.

Example A3: Cell Proliferation Assay

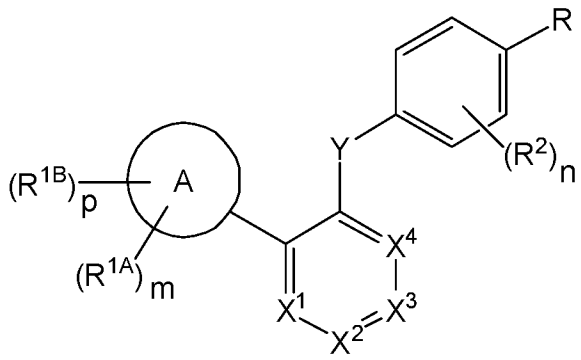
[00425] Cancer cell lines are plated in 384-well plates 24 hrs before drug treatment. Post incubation for various time periods with the test compounds, starting from 3 μM (final concentration in assay plate), 1:3 dilution, and 10 points in duplicates, the number of viable cells and proliferative cells are determined using CellTiter-Glo® Luminescent Cell Viability Assay Kit (Promega) and Click-iT EdU HCS Assay Kit (Invitrogen) according to the manufacturers' protocols. The IC_{50} values and maximum % inhibition of the test compounds are calculated using the dose response curves.

[00426] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I)

wherein,

ring A is fused bicyclic heteroaryl;

X^1 is N or CR^{X1}; X^2 is N or CR^{X2}; X^3 is N or CR^{X3}; X^4 is N or CR^{X4};

Y is CR^4R^5, O, S, or NR^6;

each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, nitro, $-OR^7$, $-SR^7$, -CN, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

R is halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(R^7)_5$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-C(=O)OR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-NR^7R^8$, $-NR^7S(=O)_2R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl;

each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl;

each R^2 is independently halogen, nitro, -CN, $-OR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, $-NR^7R^8$, $-C(=O)R^7$, $-C(=O)OR^7$, $-C(=O)NR^7R^8$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted

or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each R^4, R^5, R^6, R^7, and R^8 is independently hydrogen, halogen, -CN, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_2-C_6alkenyl, substituted or unsubstituted C_2-C_6alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted 3- to 10-membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; or

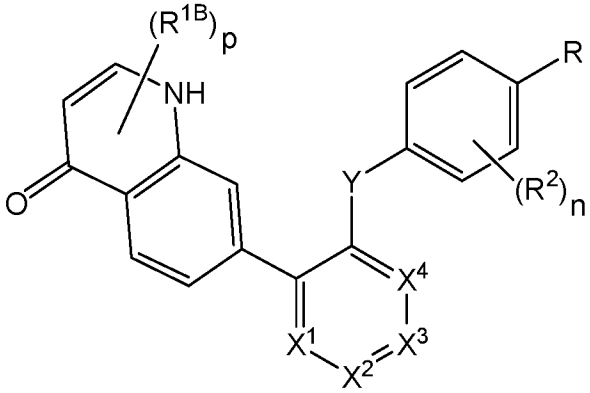
R^4 and R^5 taken together with the atom to which they are attached to form a substituted or unsubstituted C_3-C_8cycloalkyl or substituted or unsubstituted 3- to 8-membered heterocycloalkyl having 1 or 2 heteroatoms each independently selected from N, O, and S; or

R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S; and

each of m, n, and p is independently 0, 1, 2, 3, or 4.

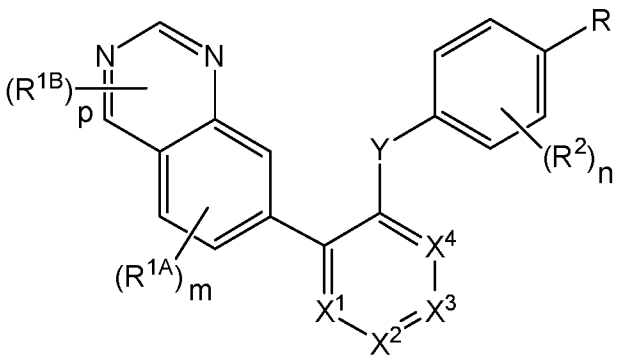
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 8- to 12- membered fused bicyclic heteroaryl.
3. The compound of claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein ring A is 9- to 11- membered fused bicyclic heteroaryl.
4. The compound of any one of claims 1-3, wherein ring A is 6/5-fused, 6/6-fused, or 6/7-fused bicyclic heteroaryl.
5. The compound of any one of claims 1-4, ring A is 6/5-fused or 6/6-fused bicyclic heteroaryl.
6. The compound of any one of claims 1-5, wherein ring A is 6/6-fused bicyclic heteroaryl.
7. The compound of any one of claims 1-6, wherein ring A is fused bicyclic heteroaryl having 1-6 heteroatoms, each independently selected from N, O, and S.
8. The compound of any one of claims 1-7, wherein ring A is fused bicyclic heteroaryl having 0-5 N atoms, 0-2 O atoms, and 0-2 S atoms.
9. The compound of any one of claims 1-8, wherein ring A is fused bicyclic heteroaryl having 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms.
10. The compound of any one of claims 1-9, wherein ring A is fused bicyclic heteroaryl having 0-3 N atoms and 0-1 O atom.
11. The compound of any one of claims 1-8, wherein ring A is fused bicyclic heteroaryl having 1-5 N atoms.

12. The compound of any one of claims 1-9 or 11, wherein ring A is fused bicyclic heteroaryl having 1-4 N atoms.
13. The compound of any one of claims 1-12, wherein ring A is fused bicyclic heteroaryl having 2 N atoms.
14. The compound of any one of claims 1-12, wherein ring A is fused bicyclic heteroaryl having 3 N atoms.
15. The compound of any one of claims 1-4, wherein ring A is 6/5-fused bicyclic heteroaryl selected from benzofuranyl, benzothiophenyl, indolyl, isoindolyl, benzoisoxazolyl, benzooxazolyl, benzoisothiazolyl, benzothiazolyl, indazolyl, benzoimidazolyl, benzotriazolyl, benzooxadiazolyl, benzothiadiazolyl, pyrazolopyridinyl, imidazopyridinyl, and triazolopyridinyl.
16. The compound of any one of claims 1-4, wherein ring A is 6/5-fused bicyclic heteroaryl is selected from triazolopyridinyl, benzoisoxazolyl, triazolopyridinyl, benzotriazolyl, benzoimidazolyl, triazolopyridinyl, and imidazopyridinyl.
17. The compound of any one of claims 1-4, wherein ring A is 6/6-fused bicyclic heteroaryl selected from quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyridopyridazinyl, pyridopyrimidinyl, pyridopyrazinyl, pyrimidopyrimidinyl, and pyrazinopyrazinyl.
18. The compound of any one of claims 1-4, wherein ring A is 6/6-fused bicyclic heteroaryl selected from quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, and naphthyridinyl.
19. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-a), or a pharmaceutically acceptable salt or solvate thereof:



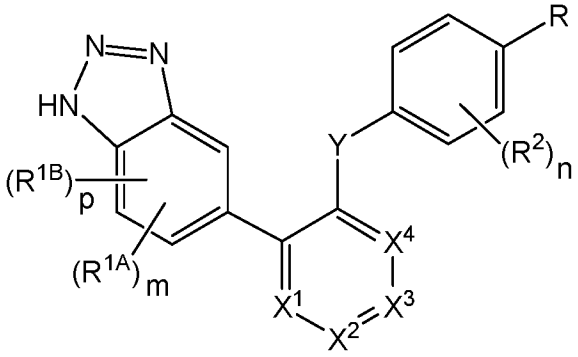
Formula (II-a).

20. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-b), or a pharmaceutically acceptable salt or solvate thereof:



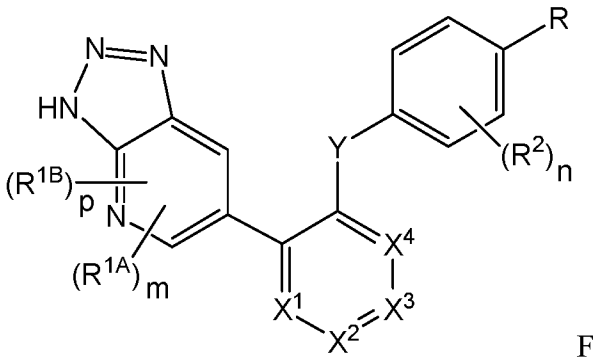
Formula (II-b).

21. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-c), or a pharmaceutically acceptable salt or solvate thereof:



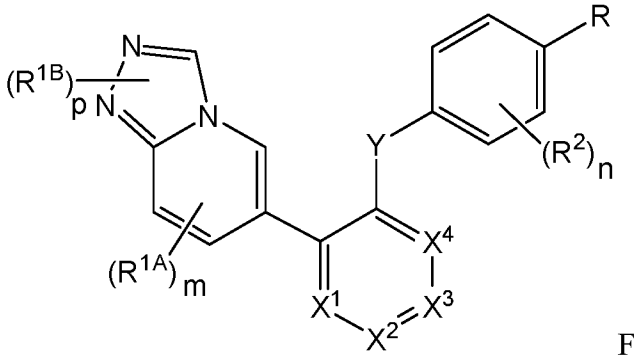
Formula (II-c).

22. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-d), or a pharmaceutically acceptable salt or solvate thereof:



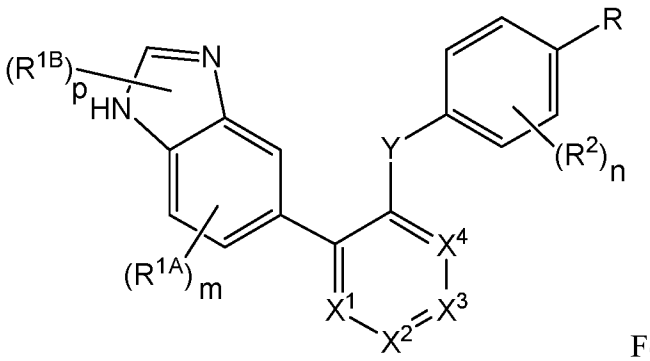
Formula (II-d).

23. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-e), or a pharmaceutically acceptable salt or solvate thereof:



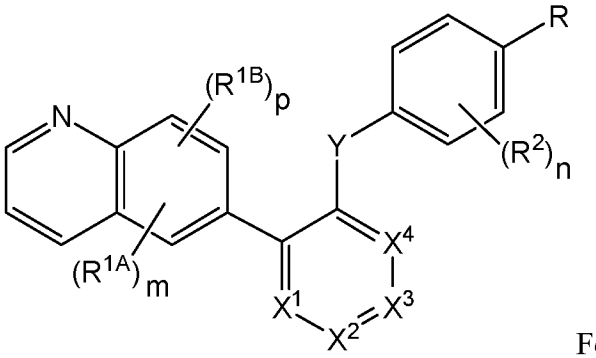
Formula (II-e).

24. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-f), or a pharmaceutically acceptable salt or solvate thereof:



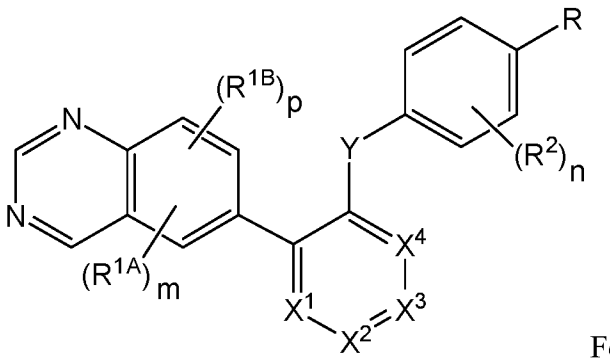
Formula (II-f).

25. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-g), or a pharmaceutically acceptable salt or solvate thereof:



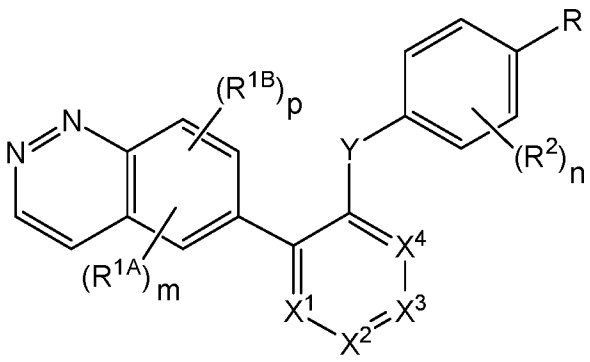
Formula (II-g).

26. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-h), or a pharmaceutically acceptable salt or solvate thereof:



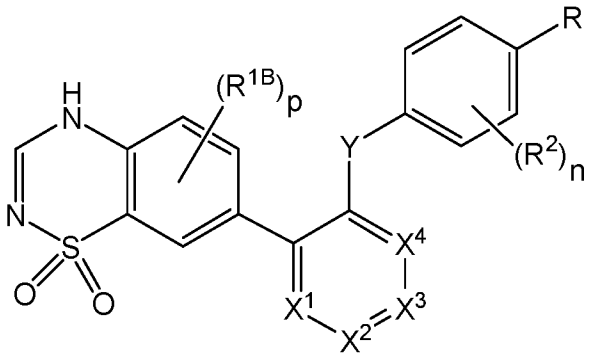
Formula (II-h).

27. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-i), or a pharmaceutically acceptable salt or solvate thereof:



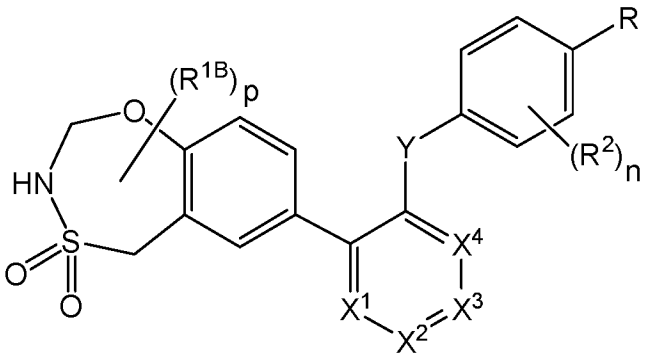
Formula (II-i).

28. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-j), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-j).

29. The compound of any one of claim 1-4, wherein the compound has a structure of Formula (II-k), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II-k).

30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}.

31. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is CR^{X4}.

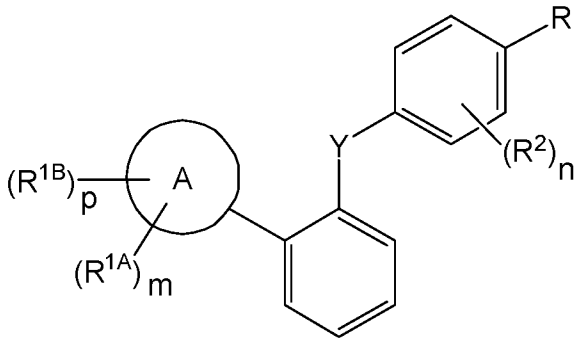
32. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is N; X^3 is CR^{X3}; and X^4 is CR^{X4}.

33. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is N; and X^4 is CR^{X4}.

34. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N.

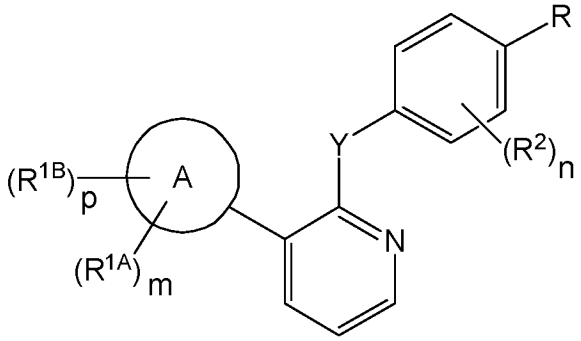
35. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is CR^{X3}; and X^4 is N.
36. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^{X1}; X^2 is N; X^3 is N; and X^4 is CR^{X4}.
37. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is N; X^3 is CR^{X3}; and X^4 is N.
38. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N; X^2 is CR^{X2}; X^3 is N; and X^4 is N.
39. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_2-C_4alkenyl, substituted or unsubstituted C_2-C_4alkynyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl.
40. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, halogen, $-OR^7$, $-SR^7$, -CN, $-NR^7R^8$, substituted or unsubstituted C_1-C_4alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_7cycloalkyl, or substituted or unsubstituted 3- to 8-membered heterocycloalkyl.
41. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH(OH)CH_3$, $-CH_2CN$, $-CH_2C(=O)OH$, $-CH_2C(=O)OCH_3$, $-CH_2C(=O)OCH_2CH_3$, $-CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2NH_2$, $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH=CH_2$, $-C\equiv CH$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-C(=O)N(CH_3)_2$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHC(=O)OCH_3$, $-N(CH_3)C(=O)OCH_3$, $-S(=O)CH_3$, $-S(=O)_2CH_3$, $-NHS(=O)_2CH_3$, or $-N(CH_3)S(=O)_2CH_3$.
42. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-C\equiv CH$, $-OCH_3$, $-NH_2$, $-NHC(=O)CH_3$, $-N(CH_3)C(=O)CH_3$, $-NHS(=O)_2CH_3$, $-N(CH_3)S(=O)_2CH_3$, $-S(=O)CH_3$, or $-S(=O)_2CH_3$.

43. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, Br, I, $-CH_3$, $-CH_2CH_3$, cyclopropyl, $-OCH_3$, or $-OCF_3$.
44. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen, F, Cl, or $-CH_3$.
45. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is independently hydrogen or F.
46. The compound of any one of claims 1-38, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^{X1}, R^{X2}, R^{X3}, and R^{X4}, when present, is hydrogen.
47. The compound of any one of claim 1-18 or 30, wherein the compound has a structure of Formula (III-a), or a pharmaceutically acceptable salt or solvate thereof:



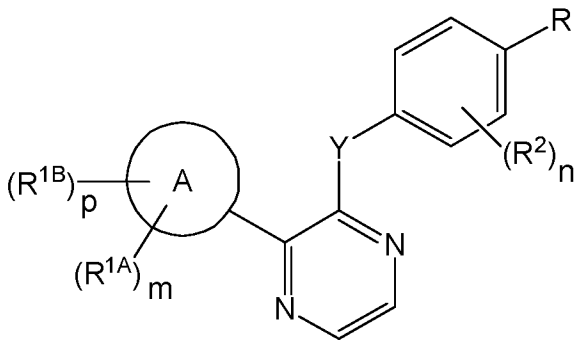
Formula (III-a).

48. The compound of any one of claim 1-18 or 34, wherein the compound has a structure of Formula (III-b), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-b).

49. The compound of any one of claim 1-18 or 35, wherein the compound has a structure of Formula (III-c), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III-c).

50. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently halogen, oxo, nitro, -CN, -OR^7, -SR^7, -S(=O)R^7, -$S(=O)_2R^7$, -$S(=O)_2NR^7R^8$, -NR^7R^8, -C(=O)R^7, -C(=O)OR^7, -C(=O)NR^7R^8, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl.

51. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently halogen, oxo, -CN, -OR^7, -SR^7, -S(=O)R^7, -$S(=O)_2R^7$, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl.

52. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, Br, I, =O, -CH_3, -CH_2CH_3, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2OH$, -$CH(OH)CH_3$, -$CH_2CH(OH)CH_3$, -$C(CH_3)_2OH$, -$CH_2CH(OH)CH_2OH$, -CH_2CN, -$CH_2C(=O)OH$, -$CH_2C(=O)OCH_3$, -$CH_2C(=O)OCH_2CH_3$, -$CH_2C(=O)NH_2$, -$CH_2CH_2C(=O)NH_2$, -$CH_2C(=O)NHCH_3$, -$CH_2C(=O)N(CH_3)_2$, -CH_2NH_2, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CHFCH_3$, -CF_2CH_3, -$CH=CH_2$, -C≡CH, -OH, -OCH_3, -OCH_2CH_3, -OCH_2F, -$OCHF_2$, -OCF_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, cyclopropyl, cyclobutyl, cyclopentyl, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, or oxetan-3-yl.

53. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, =O, -CH_3, -CH_2CH_3, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2OH$, -$CH(OH)CH_3$, -$CH_2CH(OH)CH_3$, -$C(CH_3)_2OH$, -$CH_2CH(OH)CH_2OH$, -CH_2CN, -$CH_2C(=O)OH$, -$CH_2C(=O)OCH_3$, -$CH_2C(=O)OCH_2CH_3$, -$CH_2C(=O)NH_2$, -$CH_2CH_2C(=O)NH_2$, -$CH_2C(=O)NHCH_3$, -$CH_2C(=O)N(CH_3)_2$, -CH_2NH_2, -$CH_2CH_2NH_2$, -$CH_2CH_2CH_2NH_2$, -CH_2NHCH_3, -$CH_2N(CH_3)_2$, -CH_2F, -CHF_2, -CF_3, -CH_2CH_2F, -CH_2CHF_2, -CH_2CF_3, -$CHFCH_3$, -CF_2CH_3, -$CH=CH_2$, -C≡CH, -OH, -OCH_3, -OCH_2CH_3, -OCH_2F, -$OCHF_2$, -OCF_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, or oxetan-3-yl.

54. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, =O, -CH_3, -CH_2CH_3, -CH_2OH, -CH_2CH_2OH, -$CH_2CH_2CH_2OH$, -$CH(CH_3)CH_2OH$, -

$CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, $-CHFCH_3$, $-CF_2CH_3$, $-CH=CH_2$, $-C\equiv CH$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, or oxetan-3-yl.

55. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CH_2F$, $-CH_2CHF_2$, $-CH_2CF_3$, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, or oxetan-3-yl.

56. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, $-CH_2OH$, $-CH_2CH_2OH$, $-C(CH_3)_2OH$, $-CH_2CH(OH)CH_2OH$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

57. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently F, Cl, =O, $-CH_3$, $-CH_2CH_3$, or $-OCH_3$.

58. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently -OH, $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$, $-CH(CH_3)CH_2OH$, $-CH(OH)CH_3$, $-CH_2CH(OH)CH_3$, $-C(CH_3)_2OH$, or $-CH_2CH(OH)CH_2OH$.

59. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently $-CH_2C(=O)NH_2$, $-CH_2CH_2C(=O)NH_2$, $-CH_2C(=O)NHCH_3$, or $-CH_2C(=O)N(CH_3)_2$.

60. The compound of any one of claims 1-49, wherein each R^{1A} and R^{1B} is independently $-OCH_3$, $-OCH_2CH_3$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, or oxetan-3-yl.

61. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt or solvate thereof, wherein each m and p is independently is 0, 1, or 2.

62. The compound of any one of claims 1-60, or a pharmaceutically acceptable salt or solvate thereof, wherein each m and p is 1.

63. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2 and p is 0, 1 or 2.

64. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 2 and p is 0 or 1.

65. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein m is 0 and p is 1.

66. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt or solvate thereof, wherein each m and p is 0.

67. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is halogen, nitro, -CN, -OR^7, -SR^7, -$S(R^7)_5$, -$C(=O)R^7$, -$C(=O)NR^7R^8$, -$C(=O)OR^7$, -$S(=O)R^7$, -$S(=O)_2R^7$, -$NR^7S(=O)_2R^8$, -$NR^7C(=O)R^8$, -$NR^7C(=O)OR^8$, or substituted or unsubstituted C_1-C_6fluoroalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted 3- to 10-membered heterocycloalkyl; or R^7 and R^8 taken together with the atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

68. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, Br, I, nitro, -CN, -SF_5, -SCF_3, -OCH_2F, -$OCHF_2$, -OCF_3, -$C(=O)CH_3$, -$C(=O)OCH_3$ -$C(=O)NH_2$, -$C(=O)NHCH_3$, -$C(=O)N(CH_3)_2$, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$NHS(=O)_2CH_3$, -$N(CH_3)S(=O)_2CH_3$, -$NHC(=O)CH_3$, -$N(CH_3)C(=O)CH_3$, -$NHC(=O)OCH_3$, -$N(CH_3)C(=O)OCH_3$, -CH_2F, -CHF_2, or -CF_3.

69. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, -CN, -OCF_3, -CHF_2, -SCF_3, or -CF_3.

70. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, -OCF_3, -CHF_2, -SCF_3, or -CF_3.

71. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, -SF_5, -SCF_3, or -CF_3.

72. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is F, Cl, -SF_5, -OCF_3, -SCF_3, or -CF_3.

73. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is -CF_3.

74. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is -OCF_3.

75. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is -SF_5.

76. The compound of any one of claims 1-66, or a pharmaceutically acceptable salt or solvate thereof, wherein R is -SCF_3.

77. The compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently halogen, nitro, -CN, -OR^7, -SR^7, -$S(=O)_2R^7$, -

NR^7R^8, -C(=O)OR^7, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_1-C_6fluoroalkyl; and

each R^7 and R^8 is independently hydrogen, substituted or unsubstituted C_1-C_6alkyl, substituted or unsubstituted C_1-C_6fluoroalkyl, or substituted or unsubstituted C_1-C_6heteroalkyl; or R^7 and R^8 on the same nitrogen atom are optionally taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted N-containing 3- to 8-membered heterocycloalkyl optionally having 1 or 2 additional heteroatoms each independently selected from N, O, and S.

78. The compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, Br, -CN, -OH, $-OCH_3$, $-OCH_2CH_3$, $-OCH_2CH_2OH$, $-OCH_2CN$, $-OCF_3$, $-S(=O)_2CH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-C(=O)OCH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_2F$, $-CHF_2$, or $-CF_3$.

79. The compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, -CN, $-OCH_3$, $-OCF_3$, $-C(=O)OCH_3$, $-CH_3$, or $-CF_3$.

80. The compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F, Cl, $-OCF_3$, or $-CF_3$.

81. The compound of any one of claims 1-76, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently F or Cl.

82. The compound of any one of claims 1-81, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0, 1, or 2.

83. The compound of any one of claims 1-82, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0 or 1.

84. The compound of any one of claims 1-83, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

85. The compound of any one of claims 1-83, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1.

86. The compound of any one of claims 1-85, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is CR^4R^5.

87. The compound of claim 86, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 and R^5 is independently hydrogen or C_1-C_4 alkyl.

88. The compound of claim 86, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 and R^5 is hydrogen.

89. The compound of any one of claims 1-85, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is O.
90. The compound of any one of claims 1-85, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is S.
91. The compound of any one of claims 1-85, or a pharmaceutically acceptable salt or solvate thereof, wherein Y is NR^6.
92. The compound of claim 91, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is hydrogen or C_1-C_4 alkyl.
93. The compound of claim 91, or a pharmaceutically acceptable salt or solvate thereof, wherein R^6 is hydrogen.
94. A compound or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is a compound from Table 1.
95. A pharmaceutical composition comprising the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-94, and a pharmaceutically acceptable excipient.
96. A method of inhibiting one or more of proteins encompassed by, or related to, the Hippo pathway in a subject, comprising administering to a subject the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-94, or a pharmaceutical composition of claim 95.
97. A method of inhibiting transcriptional coactivator with PDZ binding motif/Yes-associated protein transcriptional coactivator (TAZ/YAP) in a subject comprising administering to a subject the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-94, or a pharmaceutical composition of claim 95.
98. The method of claim 96 or claim 97, wherein the subject has cancer, polycystic kidney disease or liver fibrosis.
99. The method of claim 98, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.
100. A method of treating cancer in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-94, or a pharmaceutical composition of claim 95.

101. The method of claim 100, wherein the cancer is selected from mesothelioma, hepatocellular carcinoma, meningioma, malignant peripheral nerve sheath tumor, Schwannoma, lung cancer, bladder carcinoma, cutaneous neurofibromas, prostate cancer, pancreatic cancer, glioblastoma, endometrial adenosquamous carcinoma, anaplastic thyroid carcinoma, gastric adenocarcinoma, esophageal adenocarcinoma, ovarian cancer, ovarian serous adenocarcinoma, melanoma, and breast cancer.
102. A method of treating polycystic kidney disease or liver fibrosis in a subject in need thereof comprising administering to the subject in need thereof a therapeutically effective amount of the compound or pharmaceutically acceptable salt or solvate of any one of claims 1-94, or a pharmaceutical composition of claim 95.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/013747

A. CLASSIFICATION OF SUBJECT MATTER

C07D 215/233(2006.01)i; **C07D 239/30**(2006.01)i; **C07D 403/04**(2006.01)i; **C07D 471/04**(2006.01)i; **C07D 417/04**(2006.01)i; **A61K 31/47**(2006.01)i; **A61K 31/517**(2006.01)i; **A61P 35/00**(2006.01)i; **A61P 13/12**(2006.01)i; **A61P 1/16**(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 215/233(2006.01); A61K 31/352(2006.01); A61K 31/444(2006.01); C07D 213/643(2006.01); C07D 213/65(2006.01); C07D 311/30(2006.01); C07D 471/04(2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN(Registry,CAplus) & Keywords: phenyl, fused bicyclic heteroaryl, YAP, TAZ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021-247634 A1 (DANA-FARBER CANCER INSTITUTE, INC.) 09 December 2021 claims 122, 126, 127; page 248	1-3,94
X	CN 104230869 A (SECOND MILITARY MEDICAL UNIVERSITY, PLA et al.) 24 December 2014 (2014-12-24) claims 1, 7-9; table 1 (compound 64)	1-3,94
X	US 2014-0275026 A1 (ABBVIE INC.) 18 September 2014 (2014-09-18) claims 1, 28; example 77	1-3,94
X	US 2019-0055199 A1 (KAKEN PHARMACEUTICAL CO., LTD.) 21 February 2019 (2019-02-21) table 63 (compound I-514)	1-3
X	JP 2018-145180 A (KAKEN PHARMACEUTICAL CO., LTD.) 20 September 2018 (2018-09-20) table 63 (compound I-514)	1-3

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2022	**24 October 2022**

Name and mailing address of the ISA/KR	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2022/013747

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **96-102**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 96-102 pertain to methods for treatment of the human body by surgery or therapy as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☑ Claims Nos.: **87, 88, 92, 93, 99, 101**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 87, 88, 92, 93, 99 and 101 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☑ Claims Nos.: **4-86, 89-91, 95-98, 100, 102**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/US2022/013747

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2021-247634	A1		None			
CN	104230869	A	24 December 2014	CN	104230869	B	07 December 2016
US	2014-0275026	A1	18 September 2014	AU	2014-248663	A1	24 September 2015
				BR	112015022643	A2	18 July 2017
				CA	2905071	A1	09 October 2014
				CN	105164130	A	16 December 2015
				EP	2970276	A1	20 January 2016
				HK	1218909	A1	17 March 2017
				IL	241123	A	30 November 2015
				JP	2016-512543	A	28 April 2016
				KR	10-2015-0126696	A	12 November 2015
				MX	2015011984	A	15 December 2015
				RU	2015143191	A	18 April 2017
				SG	11201507383	A	29 October 2015
				TW	201443051	A	16 November 2014
				US	2016-0237084	A1	18 August 2016
				US	9321764	B2	26 April 2016
				WO	2014-165143	A1	09 October 2014
				ZA	201506575	B	29 May 2019
US	2019-0055199	A1	21 February 2019	AR	106047	A1	06 December 2017
				AU	2016-325143	A1	10 May 2018
				AU	2016-325143	B2	13 August 2020
				BR	112018004447	A2	25 September 2018
				CA	2997537	A1	23 March 2017
				CN	108290838	A	17 July 2018
				CN	108290838	B	31 December 2021
				EP	3351533	A1	25 July 2018
				HK	1256486	A1	27 September 2019
				IL	258160	A	01 January 2022
				JP	2019-070023	A	09 May 2019
				JP	6469238	B2	13 February 2019
				JP	6868650	B2	12 May 2021
				KR	10-2018-0052635	A	18 May 2018
				MX	2018003318	A	16 May 2018
				PH	12018500434	A1	03 September 2018
				RU	2018114077	A	18 October 2019
				RU	2018114077	A3	06 February 2020
				RU	2760373	C2	24 November 2021
				SG	11201801856	A	27 April 2018
				TW	201718545	A	01 June 2017
				TW	I730002	B	11 June 2021
				US	10647675	B2	12 May 2020
				WO	2017-047602	A1	23 March 2017
JP	2018-145180	A	20 September 2018	JP	2019-073537	A	16 May 2019
				JP	6469272	B2	13 February 2019